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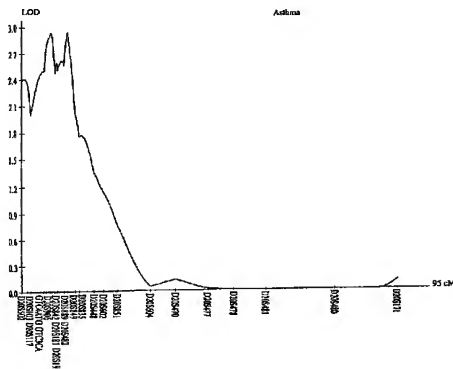
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(54) Title: NOVEL HUMAN GENE RELATING TO RESPIRATORY DISEASES, OBESITY, AND INFLAMMATORY BOWEL DISEASE



(57) Abstract: This invention relates to genes identified from human chromosome 20p13-p12, which are associated with various diseases, including asthma. The invention also relates to the nucleotide sequences of these genes, isolated nucleic acids comprising these nucleotide sequences, and isolated polypeptides or peptides encoded thereby. The invention further relates to vectors and host cells comprising the disclosed nucleotide sequences, or fragments thereof, as well as antibodies that bind to the encoded polypeptides or peptides. Also related are ligands that modulate the activity of the disclosed genes or gene products. In addition, the invention relates to methods and compositions employing the disclosed nucleic acids, polypeptides or peptides, antibodies, and/or ligands for use in diagnostics and therapeutics for asthma and other diseases.

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**NOVEL HUMAN GENE RELATING TO RESPIRATORY DISEASES,  
OBESITY, AND INFLAMMATORY BOWEL DISEASE**

**5     RELATED APPLICATIONS**

This application is a continuation-in-part of U.S. Application Serial Number 09/834,597, filed April 13, 2001, and International Application No. PCT/US01/12245, filed April 13, 2001.

**FIELD OF THE INVENTION**

10       This invention relates to genes identified from human chromosome 20p13-p12, including Gene 216, which are associated with asthma, obesity, inflammatory bowel disease, and other human diseases. The invention also relates to the nucleotide sequences of these genes, including genomic DNA sequences, cDNA sequences, single nucleotide polymorphisms, alleles, and

15     haplotypes. The invention further relates to isolated nucleic acids comprising these nucleotide sequences, and isolated polypeptides or peptides encoded thereby. Also related are expression vectors and host cells comprising the disclosed nucleic acids or fragments thereof, as well as antibodies that bind to the encoded polypeptides or peptides. The present invention further relates

20     to ligands that modulate the activity of the disclosed genes or gene products.

In addition, the invention relates to diagnostics and therapeutics for various diseases, including asthma, utilizing the disclosed nucleic acids, polypeptides or peptides, antibodies, and/or ligands.

**BACKGROUND**

25       Mouse chromosome 2 has been linked to a variety of disorders including airway hyperresponsiveness and obesity (DeSanctis et al., 1995, *Nature Genetics*, **11**:150-154; Nagle et al., 1999, *Nature*, **398**:148-152). This region of the mouse genome is homologous to portions of human chromosome 20 including 20p13-p12. Although human chromosome 20p13-12p has been

30     linked to a variety of genetic disorders including diabetes insipidus, neurohypophyseal, congenital endothelial dystrophy of cornea, insomnia,

neurodegeneration with brain iron accumulation 1 (Hallervorden-Spatz syndrome), fibrodysplasia ossificans progressiva, alagille syndrome, hydrometrocolpos (McKusick-Kaufman syndrome), Creutzfeldt-Jakob disease and Gerstmann-Straussler disease (see NCBI; National Center for  
5 Biotechnology Information, National Library of Medicine, 38A, 8N905, 8600 Rockville Pike, Bethesda, MD 20894; on the world wide web at ncbi.nlm.nih.gov) the genes affecting these disorders have yet to be discovered. There is a need in the art for identifying specific genes relating to these disorders, as well as genes associated with obesity, lung disease,  
10 particularly, inflammatory lung disease phenotypes such as Chronic Obstructive Lung Disease (COPD), Adult Respiratory Distress Syndrome (ARDS), and asthma. Identification and characterization of such genes will make possible the development of effective diagnostics and therapeutic means to treat lung-related disorders.

15       **SUMMARY OF THE INVENTION**

This invention relates to Gene 216 located on human chromosome 20p13-p12. In specific embodiments, the invention relates to isolated nucleic acids comprising Gene 216 genomic sequences (e.g., SEQ ID NO:5 and SEQ ID NO:6), cDNA sequences (e.g., SEQ ID NO:1 and SEQ ID NO:3),  
20 orthologous sequences (e.g., SEQ ID NO:364 and SEQ ID NO:365), complementary sequences, sequence variants, or fragments thereof, as described herein. The present invention also encompasses nucleic acid probes or primers useful for assaying a biological sample for the presence or expression of Gene 216. The invention further encompasses nucleic acids  
25 variants comprising alleles or haplotypes of single nucleotide polymorphisms (SNPs) identified in several genes, including Gene 216 (e.g., SEQ ID NO:241-288, and SEQ ID NO:373-420, and fragments thereof). Nucleic acid variants comprising SNP alleles or haplotypes can be used to diagnose diseases such as asthma, or to determine a genetic predisposition thereto. In addition, the  
30 present invention encompasses nucleic acids comprising alternate splicing variants (e.g., SEQ ID NO:2 and SEQ ID NO:350-362).

This invention also relates to vectors and host cells comprising vectors comprising the Gene 216 nucleic acid sequences disclosed herein. Such vectors can be used for nucleic acid preparations, including antisense nucleic acids, and for the expression of encoded polypeptides or peptides. Host cells  
5 can be prokaryotic or eukaryotic cells. In specific embodiments, an expression vector comprises a DNA sequence encoding the Gene 216 polypeptide sequence (e.g., SEQ ID NO:4 or SEQ ID NO:363), orthologous polypeptides (e.g., SEQ ID NO:366), sequence variants, or fragments thereof, as described herein.

10 The present invention further relates to isolated Gene 216 polypeptides and peptides. In specific embodiments, the polypeptides or peptides comprise the amino acid sequence of the Gene 216 (e.g., SEQ ID NO:4 or SEQ ID NO:363), orthologous polypeptides (e.g., SEQ ID NO:366), sequence variants, or portions thereof, as described herein. In addition, this invention  
15 encompasses isolated fusion proteins comprising Gene 216 polypeptides or peptides.

The present invention also relates to isolated antibodies, including monoclonal and polyclonal antibodies, and antibody fragments, that are specifically reactive with the Gene 216 polypeptides, fusion proteins, or  
20 variants, or portions thereof, as disclosed herein. In specific embodiments, monoclonal antibodies are prepared to be specifically reactive with the Gene 216 polypeptide (e.g., SEQ ID NO:4 or SEQ ID NO:363), orthologous polypeptides (e.g., SEQ ID NO:366), or peptides, or sequence variants thereof.

In addition, the present invention relates to methods of obtaining Gene  
25 216 polynucleotides and polypeptides, variant sequences, or fragments thereof, as disclosed herein. Also related are methods of obtaining anti-Gene 216 antibodies and antibody fragments. The present invention also encompasses methods of obtaining Gene 216 ligands, e.g., agonists, antagonists, inhibitors, and binding factors. Such ligands can be used as  
30 therapeutics for asthma and related diseases.

The present invention also relates to diagnostic methods and kits

utilizing Gene 216 (wild-type, mutant, or variant) nucleic acids, polypeptides, antibodies, or functional fragments thereof. Such factors can be used, for example, in diagnostic methods and kits for measuring expression levels of Gene 216, and to screen for various Gene 216-related diseases, especially  
5 asthma. In addition, the nucleic acids described herein can be used to identify chromosomal abnormalities affecting Gene 216, and to identify allelic variants or mutations of Gene 216 in an individual or population.

The present invention further relates to methods and therapeutics for the treatment of various diseases, including asthma. In various embodiments,  
10 therapeutics comprising the disclosed Gene 216 nucleic acids, polypeptides, antibodies, ligands, or variants, derivatives, or portions thereof, are administered to a subject to treat, prevent, or ameliorate asthma. Specifically related are therapeutics comprising Gene 216 antisense nucleic acids, monoclonal antibodies, metalloprotease inhibitors, and gene therapy vectors.  
15 Such therapeutics can be administered alone, or in combination with one or more asthma treatments.

In addition, this invention relates to non-human transgenic animals and cell lines comprising one or more of the disclosed Gene 216 nucleic acids, which can be used for drug screening, protein production, and other purposes.  
20 Also related are non-human knock-out animals and cell lines, wherein one or more endogenous Gene 216 genes (i.e., orthologs), or portions thereof, are deleted or replaced by marker genes.

This invention further relates to methods of identifying proteins that are candidates for being involved in asthma (i.e., a "candidate protein"). Such  
25 proteins are identified by a method comprising: 1) identifying a protein in a first individual having the asthma phenotype; 2) identifying a protein in a second individual not having the asthma phenotype; and 3) comparing the protein of the first individual to the protein of the second individual, wherein a) the protein that is present in the second individual but not the first individual is the  
30 candidate protein; or b) the protein that is present in a higher amount in the second individual than in the first individual is the candidate protein; or c) the

protein that is present in a lower amount in the second individual than in the first individual is the candidate protein.

#### **BRIEF DESCRIPTION OF THE FIGURES**

**Figure 1** depicts the LOD Plot of Linkage to Asthma.

5        **Figure 2** depicts the LOD Plot of Linkage to BHR (PC20  $\leq$  4 mg/ml) & Asthma.

**Figure 3** depicts the LOD Plot of Linkage to BHR (PC20  $\leq$  16 mg/ml) & Asthma

**Figure 4** depicts the LOD Plot of Linkage to High Total IgE & Asthma

10        **Figure 5** depicts the LOD Plot of Linkage to High Specific IgE & Asthma

**Figure 6** depicts the BAC/STS content contig map of human chromosome 20p13-p12.

**Figure 7** depicts the BAC1098L22 nucleotide sequence (SEQ ID NO:5).

15        **Figure 8** depicts the locations of single nucleotide polymorphisms, corresponding amino acid changes, and domains in the Gene 216 transcript. The exons of the transcript are marked from A to V and the size of each one is indicated. Above the exons, the 8 domains are labeled and a black bar represents the approximate location of each one. Underneath the black bars are the approximate location of the amino acid changes that have been identified. The amino acids boxed in white are the alleles that are most frequently observed. The nucleotides boxed in gray are the alleles that are most frequently observed. Single nucleotide polymorphisms are unboxed, and the polymorphism names appear underneath. The uterus cDNA clone does not contain all of Exon A, and does not contain the sequence CAG between  
20        Exon U and V.  
25

**Figure 9** depicts alternate splice variants of Gene 216 obtained from lung tissue, including rt672 (SEQ ID NO:350), rt690 (SEQ ID NO:351), rt709 (SEQ ID NO:352), rt711 (SEQ ID NO:353), rt713 (SEQ ID NO:354), and rt720 (SEQ ID NO:355).

30        **Figure 10** depicts alternate splice variants of Gene 216 obtained from lung tissue, including rt725 (SEQ ID NO:356), rt727 (SEQ ID NO:357), rt733

(SEQ ID NO:358), rt735 (SEQ ID NO:359), rt764 (SEQ ID NO:360), rt772 (SEQ ID NO:361), and rt774 (SEQ ID NO:362).

**Figure 11** depicts the structure of the genomic sequence of Gene 216.

**Figure 12** depicts the alternate AG splice sequences at the junction of  
5 Intron UV and Exon V in Gene 216.

**Figure 13** depicts the promoter region of Gene 216. The Gene 216 promoter sequence is shown in SEQ ID NO:8; the Gene 216 enhancer sequence is shown in SEQ ID NO:7.

**Figure 14** depicts a dendrogram of the ADAM family members and the  
10 relationship of Gene 216 to ADAMs that possesses an active metalloprotease domain.

**Figure 15** depict Northern Blots illustrating Gene 216 expression patterns.

**Figure 16** depicts a Dot Blot that shows Gene 216 expression in various  
15 tissue types.

**Figure 17** depicts RT-PCR analysis of Gene 216 expression in primary cells from lung tissue.

**Figure 18** depicts an amino acid sequence alignment (Pileup) of 5 ADAM family members that are closely related to Gene 216. Amino acids  
20 highlighted in black show 100% identity within the Pileup; dark gray show 80% identity; and light gray show 60% identity. The boxed amino acids represent the cysteine switch, the metalloprotease domain, and the "met-turn". The labeled arrows show the locations of the 8 domains.

**Figure 19** depicts the amino acid sequence of Gene 216 (SEQ ID  
25 NO:4). Labeled arrows above the sequence denote domain and corresponding length. Black boxes represent the signal sequence and the transmembrane domain identified by hydrophobicity plots. The underlined cysteine residue at position 133 is predicted to be involved in the cysteine switch, the dashed box represents the metalloprotease domain, and the methionine underlined twice  
30 is the "met-turn". The gray boxes represent the signaling binding sites identified in the cytoplasmic tail. The amino acid changes corresponding to

single nucleotide polymorphisms are indicated in bold. The alanine deleted in the uterus cDNA clone is marked within a black triangle, and if present would have been between the glutamine and the aspartic acid.

**Figure 20** depicts the Kyte-Doolittle hydrophobicity plot for the Gene  
5 216 amino acid sequence.

**Figures 21** depicts the genomic sequence of the mouse ortholog of Gene 216 (SEQ ID NO:364).

**Figure 22** depicts the cDNA nucleotide sequence (SEQ ID NO:365) and predicted amino acid sequence (SEQ ID NO:366) of the mouse ortholog of  
10 Gene 216.

**Figure 23** depicts an amino acid sequence alignment (Pileup) of human Gene 216 polypeptide (SEQ ID NO:4) and the mouse ortholog of Gene 216 (SEQ ID NO:366). Vertical lines indicate identical amino acid residues. Dots indicate similar amino acid residues.

**Figure 24** depicts the nucleotide sequence (SEQ ID NO:1) and encoded amino acid sequence (SEQ ID NO:4) determined from the master cDNA sequence of Gene 216. The master cDNA sequence combines the sequence information from the uterine cDNA clone and 5'RACE clone. Identified single nucleotide polymorphism positions are underlined.  
15

**Figure 25** depicts the results of a case control study p-value plot that shows single nucleotide polymorphism association with the asthma phenotype in the combined US and UK populations.  
20

**Figure 26** depicts the results of a case control study p-value plot that shows single nucleotide polymorphism association with the asthma phenotype in the US and UK populations, separately.  
25

**Figure 27** depicts the results of a case control study p-value plot that shows single nucleotide polymorphism association with the bronchial hyper-responsiveness and asthma phenotypes in the US and UK combined population.

**Figure 28** depicts the results of a case control study p-value plot that shows single nucleotide polymorphism association with the bronchial hyper-  
30

responsiveness and asthma phenotypes in the US and UK populations, separately.

**Figure 29** depicts the genomic nucleotide sequence (SEQ ID NO:6) determined for Gene 216. Identified single nucleotide polymorphism positions are underlined.

**Figure 30** depicts the nucleotide sequence (SEQ ID NO:3) and encoded amino acid sequence (SEQ ID NO: 363) of Gene 216 determined from the uterus cDNA clone. Identified single nucleotide polymorphism positions are underlined.

**Figure 31** depicts the nucleotide sequence (SEQ ID NO:350) and encoded amino acid sequence (SEQ ID NO:337) of Gene 216 alternate splice variant rt672.

**Figure 32** depicts the nucleotide sequence (SEQ ID NO:351) and encoded amino acid sequence (SEQ ID NO:338) of Gene 216 alternate splice variant rt690.

**Figure 33** depicts the nucleotide sequence (SEQ ID NO:352) and encoded amino acid sequence (SEQ ID NO:339) of Gene 216 alternate splice variant rt709.

**Figure 34** depicts the nucleotide sequence (SEQ ID NO:353) and encoded amino acid sequence (SEQ ID NO:340) of Gene 216 alternate splice variant rt711.

**Figure 35** depicts the nucleotide sequence (SEQ ID NO:354) and encoded amino acid sequence (SEQ ID NO:341) of Gene 216 alternate splice variant rt713.

**Figure 36** depicts the nucleotide sequence (SEQ ID NO:355) and encoded amino acid sequence (SEQ ID NO:342) of Gene 216 alternate splice variant rt720.

**Figure 37** depicts the nucleotide sequence (SEQ ID NO:356) and encoded amino acid sequence (SEQ ID NO:343) of Gene 216 alternate splice variant rt725.

**Figure 38** depicts the nucleotide sequence (SEQ ID NO:357) and



encoded amino acid sequence (SEQ ID NO:344) of Gene 216 alternate splice variant rt727.

5       **Figure 39** depicts the nucleotide sequence (SEQ ID NO:358) and encoded amino acid sequence (SEQ ID NO:345) of Gene 216 alternate splice variant rt733.

**Figure 40** depicts the nucleotide sequence (SEQ ID NO:359) and encoded amino acid sequence (SEQ ID NO:346) of Gene 216 alternate splice variant rt735.

10       **Figure 41** depicts the nucleotide sequence (SEQ ID NO:360) and encoded amino acid sequence (SEQ ID NO:347) of Gene 216 alternate splice variant rt764.

**Figure 42** depicts the nucleotide sequence (SEQ ID NO:361) and encoded amino acid sequence (SEQ ID NO:348) of Gene 216 alternate splice variant rt772.

15       **Figure 43** depicts the nucleotide sequence (SEQ ID NO:362) and encoded amino acid sequence (SEQ ID NO:349) of Gene 216 alternate splice variant rt774.

#### **DETAILED DESCRIPTION OF THE INVENTION**

20       Gene 216 was identified by extensive analysis of the region of human chromosome 20p13-p12 associated with airway hyperresponsiveness, asthma, and atopy. This region has also been implicated in other diseases such as obesity (Wilson, 1999, *Arch. Intern. Med.* **159**:2513-4). Bronchial asthma, furthermore, has been linked to intestinal conditions such as inflammatory bowel disease (B. Wallaert et al., 1995, *J. Exp. Med.* **182**:1897-1904). Thus, 25 there was a need to identify and isolate the gene(s) associated with this region of human chromosome 20.

#### **Definitions**

To aid in the understanding of the specification and claims, the following definitions are provided.

30       "Disorder region" refers to a portion of the human chromosome 20 bounded by the markers D20S502 and D20S851. A "disorder-associated"

nucleic acid or polypeptide sequence refers to a nucleic acid sequence that maps to region 20p13-p12 or the polypeptides encoded therein (e.g., Gene 216 nucleic acids, and polypeptides). For nucleic acids, this encompasses sequences that are identical or complementary to the Gene 216 sequence, as well as sequence-conservative, function-conservative, and non-conservative variants thereof. For polypeptides, this encompasses sequences that are identical to the Gene 216 polypeptide, as well as function-conservative and non-conservative variants thereof. Included are naturally-occurring mutations of Gene 216 causative of respiratory diseases or obesity, such as but not limited to mutations which cause altered protein levels or stability (e.g., decreased levels, increased levels, expression in an inappropriate tissue type, increased stability, and decreased stability).

As used herein, the "reference sequence" for Gene 216 is BAC1098L22 (SEQ ID NO:5). The BAC1098L22 sequence is also the source of the disclosed Gene 216 genomic sequence (SEQ ID NO:6). "Variant" sequences refer to nucleotide sequences (and the encoded amino acid sequences) that differ from the reference sequence at one or more positions. Non-limiting examples of variant sequences include the disclosed Gene 216 single nucleotide polymorphisms (SNPs), alternate splice variants, and the amino acid sequences encoded by these variants.

The term "SNP" as used herein refers to a site in a nucleic acid sequence which contains a nucleotide polymorphism. In accordance with this invention, a SNP may comprise one of two possible "alleles". For example, SNP A-2 may comprise allele C or allele A (Table 10, below). Thus, a nucleic acid molecule comprising SNP A-2 may include a C or A at the polymorphic position. For a combination of SNPs, the term "haplotype" is used. As an example, the haplotype T/A is observed for SNP combination D1/ST+4 (Table 21, below). Thus, T is present at the polymorphic position in SNP D1 and A is present at the polymorphic position in SNP ST+4. It should be noted that the haplotype representation "T/A" does not indicate "T or A". Instead, the haplotype representation "T/A" indicates that both the T allele and the A allele

are present at their respective SNPs. In addition, the SNP representation "D1/ST+4" does not indicate "D1 or ST+4". Rather, "D1/ST+4" indicates that both SNPs are present. In some instances, a specific allele or haplotype may be associated with susceptibility to a disease or condition of interest, e.g.,  
5 asthma. In other instances, an allele or haplotype may be associated with a decrease in susceptibility to a disease or condition of interest, i.e., a protective sequence. For example, as described herein, the C allele of SNP V-1 (Example 12) and the C/A haplotype of SNPs Q-1/ST+4 (Example 13) are associated with increased susceptibility to asthma, whereas the C/G haplotype  
10 of SNPs ST+4/V-3 (Example 13) is associated with a protective effect.

"Sequence-conservative" variants are those in which a change of one or more nucleotides in a given codon position results in no alteration in the amino acid encoded at that position (i.e., silent mutations). "Function-conservative" variants are those in which a change in one or more nucleotides  
15 in a given codon position results in a polypeptide sequence in which a given amino acid residue in the polypeptide has been replaced by a conservative amino acid substitution as described in detail herein. "Function-conservative" variants also include analogs of a given polypeptide and any polypeptides that have the ability to elicit antibodies specific to a designated polypeptide. "Non-conservative" variants are those in which a change in one or more nucleotides  
20 in a given codon position results in a polypeptide sequence in which a given amino acid residue in a polypeptide has been replaced by a non-conservative amino acid substitution as described hereinbelow. "Non-conservative" variants also include polypeptides comprising non-conservative amino acid  
25 substitutions.

As used herein, the term "ortholog" denotes a gene or polypeptide obtained from one species that has homology to an analogous gene or polypeptide from a different species. The term "paralog" denotes a gene or polypeptide obtained from a given species that has homology to a distinct gene  
30 or polypeptide from that same species. For example, the disclosed mouse and human Gene 216 sequences are orthologs, whereas human Gene 216 and

human ADAM 19 are paralogs.

"Nucleic acid or "polynucleotide" as used herein refers to purine- and pyrimidine-containing polymers of any length, either polyribonucleotides or polydeoxyribonucleotide or mixed polyribo-polydeoxyribonucleotides. This includes single- and double-stranded molecules, i.e., DNA-DNA, DNA-RNA and RNA-RNA hybrids, as well as "protein nucleic acids" (PNA) formed by conjugating bases to an amino acid backbone. This also includes nucleic acids containing modified bases.

As used herein, "isolated" nucleic acids are nucleic acids separated away from other components (e.g., DNA, RNA, and protein) with which they are associated (e.g., as obtained from cells, chemical synthesis systems, or phage or nucleic acid libraries). Isolated nucleic acids are at least 60% free, preferably 75% free, and most preferably 90% free from other associated components. In accordance with the present invention, isolated nucleic acids can be obtained by methods described herein, or other established methods, including isolation from natural sources (e.g., cells, tissues, or organs), chemical synthesis, recombinant methods, combinations of recombinant and chemical methods, and library screening methods.

Nucleic acids referred to herein as "recombinant" are nucleic acids which have been produced by recombinant DNA methodology, including those nucleic acids that are generated by procedures which rely upon a method of artificial replication, such as the polymerase chain reaction (PCR) and/or cloning into a vector using restriction enzymes. Portions of recombinant nucleic acids which code for polypeptides can be identified and isolated by, for example, the method of M. Jasin et al., U.S. Patent No. 4,952,501.

A "coding sequence" or a "protein-coding sequence" is a polynucleotide sequence capable of being transcribed into mRNA and/or capable of being translated into a polypeptide or peptide. The boundaries of the coding sequence are typically determined by a translation start codon at the 5'-terminus and a translation stop codon at the 3'-terminus.

A "complement" of a nucleic acid sequence as used herein refers to the

"antisense" sequence that participates in Watson-Crick base-pairing with the original sequence.

A "probe" or "primer" refers to a nucleic acid or oligonucleotide that forms a hybrid structure with a sequence in a target region due to  
5 complementarity of the probe or primer sequence to at least one portion of the target region sequence.

Nucleic acids are "hybridizable" to each other when at least one strand of the nucleic acid can anneal to another nucleic acid strand under defined stringency conditions. Hybridization requires that the two nucleic acids contain  
10 substantially complementary sequences; depending on the stringency of hybridization, however, mismatches may be tolerated. The appropriate stringency for hybridizing nucleic acids depends on the length of the nucleic acids and the degree of complementarity, and can be determined in accordance with the methods described herein.

As used herein, "portion" and "fragment" are synonymous. A "portion" as used with regard to a nucleic acid or polynucleotide, refers to fragments of that nucleic acid or polynucleotide. The fragments can range in size from 8 nucleotides to all but one nucleotide of the entire Gene 216 sequence.  
15 Preferably, The fragments are at least 8 to 10 nucleotides in length; more preferably at least 12 nucleotides in length; still more preferably at least 15 to 20 nucleotides in length; yet more preferably at least 25 nucleotides in length; and most preferably at least 35 to 55 nucleotides in length.

"cDNA" refers to complementary or copy DNA produced from an RNA template by the action of RNA-dependent DNA polymerase (reverse transcriptase). Thus, a "cDNA clone" means a duplex DNA sequence  
25 complementary to an RNA molecule of interest, included in a cloning vector or PCR amplified. This term includes genes from which the intervening sequences have been removed.

"Cloning" refers to the use of recombination techniques to insert a particular gene or other DNA sequence into a vector molecule. In order to  
30 successfully clone a desired gene, it is necessary to use methods for

generating DNA fragments, for joining the fragments to vector molecules, for introducing the composite DNA molecule into a host cell in which it can replicate, and for selecting the clone having the target gene from amongst the recipient host cells.

5 "cDNA library" refers to a collection of recombinant DNA molecules containing cDNA inserts that together comprise essentially all of the expressed genes of an organism. A cDNA library can be prepared by methods known to one skilled in the art (see, e.g., Cowell and Austin, 1997, "cDNA Library Protocols," *Methods in Molecular Biology*). Generally, RNA is first isolated  
10 from the cells of the desired organism, and the RNA is used to prepare cDNA molecules.

"Cloning vector" refers to a plasmid or phage DNA or other DNA that is able to replicate in a host cell. The cloning vector is typically characterized by one or more endonuclease recognition sites at which such DNA sequences  
15 may be cut in a determinable fashion without loss of an essential biological function of the DNA, which may contain a marker suitable for use in the identification of cells containing the vector.

"Regulatory sequence" refers to a nucleic acid sequence that controls or regulates expression of structural genes when operably linked to those  
20 genes. These include, for example, the lac systems, the trp system, major operator and promoter regions of the phage lambda, the control region of fd coat protein and other sequences known to control the expression of genes in prokaryotic or eukaryotic cells. Regulatory sequences will vary depending on whether the vector is designed to express the operably linked gene in a  
25 prokaryotic or eukaryotic host, and may contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements and/or translational initiation and termination sites.

"Expression vector" refers to a vehicle or plasmid that is capable of expressing a gene that has been cloned into it, after transformation or  
30 integration in a host cell. The cloned gene is usually placed under the control of (i.e., operably linked to) a regulatory sequence.

"Operably linked" means that the promoter controls the initiation of expression of the gene. A promoter is operably linked to a sequence of proximal DNA if upon introduction into a host cell the promoter determines the transcription of the proximal DNA sequence(s) into one or more species of RNA. A promoter is operably linked to a DNA sequence if the promoter is capable of initiating transcription of that DNA sequence.

"Host" includes prokaryotes and eukaryotes. The term includes an organism or cell that is the recipient of an expression vector (e.g., autonomously replicating or integrating vector).

"Amplification" of nucleic acids refers to methods such as polymerase chain reaction (PCR), ligation amplification (or ligase chain reaction, LCR) and amplification methods based on the use of Q-beta replicase. These methods are well known in the art and described, for example, in U.S. Patent Nos. 4,683,195 and 4,683,202. Reagents and hardware for conducting PCR are commercially available. Primers useful for amplifying sequences from the disorder region are preferably complementary to, and preferably hybridize specifically to, sequences in the 20p13-p12 region or in regions that flank a target region therein. Gene 216 generated by amplification may be sequenced directly. Alternatively, the amplified sequence(s) may be cloned prior to sequence analysis.

"Gene" refers to a DNA sequence that encodes through its template or messenger RNA a sequence of amino acids characteristic of a specific peptide, polypeptide, or protein. The term "gene" as used herein with reference to genomic DNA includes intervening, non-coding regions, as well as regulatory regions, and can include 5' and 3' ends.

A gene sequence is "wild-type" if such sequence is usually found in individuals unaffected by the disease or condition of interest. However, environmental factors and other genes can also play an important role in the ultimate determination of the disease. In the context of complex diseases involving multiple genes ("oligogenic disease"), the "wild type", or normal sequence can also be associated with a measurable risk or susceptibility,

receiving its reference status based on its frequency in the general population. As used herein, "wild-type Gene 216" refers to the reference sequence, BAC1098L22 (SEQ ID NO:5). The wild-type Gene 216 sequence was used to identify the variants (single nucleotide polymorphisms, alleles, and haplotypes) described in detail herein.

A gene sequence is a "mutant" sequence if it differs from the wild-type sequence. For example, a Gene 216 nucleic acid containing a particular allele of a single nucleotide polymorphism may be a mutant sequence. In some cases, the individual carrying this allele has increased susceptibility toward the disease or condition of interest. In other cases, the "mutant" sequence might also refer to an allele that decreases the susceptibility toward a disease or condition of interest, and thus acts in a protective manner. Also a gene is a "mutant" gene if too much ("overexpressed") or too little ("underexpressed") of such gene is expressed in the tissues in which such gene is normally expressed, thereby causing the disease or condition of interest.

A nucleic acid or fragment thereof is "substantially homologous" to another if, when optimally aligned (with appropriate nucleotide insertions and/or deletions) with the other nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least 60% of the nucleotide bases, usually at least 70%, more usually at least 80%, preferably at least 90%, and more preferably at least 95-98% of the nucleotide bases.

Alternatively, substantial homology exists when a nucleic acid or fragment thereof will hybridize, under selective hybridization conditions, to another nucleic acid (or a complementary strand thereof). Selectivity of hybridization exists when hybridization which is substantially more selective than total lack of specificity occurs. Typically, selective hybridization will occur when there is at least about 55% sequence identity over a stretch of at least about nine or more nucleotides, preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90% (M. Kanehisa, 1984, *Nucl. Acids Res.* 11:203-213). The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will often



be over a stretch of at least 14 nucleotides, usually at least 20 nucleotides, more usually at least 24 nucleotides, typically at least 28 nucleotides, more typically at least 32 nucleotides, and preferably at least 36 or more nucleotides.

As used herein, the terms "protein" and "polypeptide" are synonymous.

- 5 "Peptides" are defined as fragments or portions of polypeptides, preferably fragments or portions having at least one functional activity (e.g., proteolysis, adhesion, fusion, antigenic, or intracellular activity) as the complete polypeptide sequence.

- 10 "Isolated" polypeptides or peptides are those that are separated from other components (e.g., DNA, RNA, and other polypeptides or peptides) with which they are associated (e.g., as obtained from cells, translation systems, or chemical synthesis systems). In a preferred embodiment, isolated polypeptides or peptides are at least 10% pure; more preferably, 80 or 90% pure. Isolated polypeptides and peptides include those obtained by methods  
15 described herein, or other established methods, including isolation from natural sources (e.g., cells, tissues, or organs), chemical synthesis, recombinant methods, or combinations of recombinant and chemical methods. Proteins or polypeptides referred to herein as "recombinant" are proteins or polypeptides produced by the expression of recombinant nucleic acids.

- 20 A "portion" as used herein with regard to a protein or polypeptide, refers to fragments of that protein or polypeptide. The fragments can range in size from 5 amino acid residues to all but one residue of the entire protein sequence. Thus, a portion or fragment can be at least 5, 5-50, 50-100, 100-200, 200-400, 400-800, or more consecutive amino acid residues of a Gene  
25 216 protein or polypeptide (e.g., SEQ ID NO:4 or SEQ ID NO:363).

An "immunogenic component", is a moiety that is capable of eliciting a humoral and/or cellular immune response in a host animal.

An "antigenic component" is a moiety that binds to its specific antibody with sufficiently high affinity to form a detectable antigen-antibody complex.

- 30 A "sample" as used herein refers to a biological sample, such as, for example, tissue or fluid isolated from an individual (including, without limitation,

plasma, serum, cerebrospinal fluid, lymph, tears, saliva, milk, pus, and tissue exudates and secretions) or from *in vitro* cell culture constituents, as well as samples obtained from, for example, a laboratory procedure.

"Antibodies" refer to polyclonal and/or monoclonal antibodies and  
5 fragments thereof, and immunologic binding equivalents thereof, that can bind to asthma proteins and fragments thereof or to nucleic acid sequences from the 20p13-p12 region, particularly from the asthma locus or a portion thereof.

The term antibody is used both to refer to a homogeneous molecular entity, or a mixture such as a serum product made up of a plurality of different  
10 molecular entities. Proteins may be prepared synthetically in a protein synthesizer and coupled to a carrier molecule and injected over several months into rabbits. Rabbit sera is tested for immunoreactivity to the protein or fragment. Monoclonal antibodies may be made by injecting mice with the proteins, or fragments thereof. Monoclonal antibodies will be screened by  
15 ELISA and tested for specific immunoreactivity with protein or fragments thereof. (Harlow et al., 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY). These antibodies will be useful in assays as well as therapeutics.

"Identity," as known in the art, is a relationship between two or more  
20 polypeptide sequences or two or more polynucleotide sequences, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between polypeptide or polynucleotide sequences, as the case may be, as determined by the match between strings of such sequences. "Identity" and "similarity" can be readily calculated by  
25 known methods, including but not limited to those described in (A.M. Lesk (ed), 1988, *Computational Molecular Biology*, Oxford University Press, NY; D.W. Smith (ed), 1993, *Biocomputing. Informatics and Genome Projects*, Academic Press, NY; A.M. Griffin and H.G. Griffin, H. G (eds), 1994, *Computer Analysis of Sequence Data*, Part I, Humana Press, NJ; G. von Heinje, 1987, *Sequence*  
30 *Analysis in Molecular Biology*, Academic Press; and M. Gribskov and J. Devereux (eds), 1991, *Sequence Analysis Primer*, M Stockton Press, NY; H.

Carillo and D. Lipman, 1988, *SIAM J. Applied Math.*, **48**:1073.

Technical and scientific terms used herein have the meanings commonly understood by one of ordinary skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies known to those of skill in the art. Publications and other materials setting forth such known methodologies to which reference is made are incorporated herein by reference in their entireties as though set forth in full.

Standard reference works setting forth the general principles of recombinant DNA technology include J. Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; P.B. Kaufman et al., (eds), 1995, *Handbook of Molecular and Cellular Methods in Biology and Medicine*, CRC Press, Boca Raton; M.J. McPherson (ed), 1991, *Directed Mutagenesis: A Practical Approach*, IRL Press, Oxford; J. Jones, 1992, *Amino Acid and Peptide Synthesis*, Oxford Science Publications, Oxford; B.M. Austen and O.M.R. Westwood, 1991, *Protein Targeting and Secretion*, IRL Press, Oxford; D.N. Glover (ed), 1985, *DNA Cloning*, Volumes I and II; M.J. Gait (ed), 1984, *Oligonucleotide Synthesis*; B.D. Hames and S.J. Higgins (eds), 1984, *Nucleic Acid Hybridization*; Wu and Grossman (eds), *Methods in Enzymology* (Academic Press, Inc.), Vol. 154 and Vol. 155; Quirke and Taylor (eds), 1991, *PCR-A Practical Approach*; Hames and Higgins (eds), 1984, *Transcription and Translation*; R.I. Freshney (ed), 1986, *Animal Cell Culture; Immobilized Cells and Enzymes*, 1986, IRL Press; Perbal, 1984, *A Practical Guide to Molecular Cloning*; J. H. Miller and M. P. Calos (eds), 1987, *Gene Transfer Vectors for Mammalian Cells*, Cold Spring Harbor Laboratory Press; M.J. Bishop (ed), 1998, *Guide to Human Genome Computing*, 2d Ed., Academic Press, San Diego, CA; L.F. Peruski and A.H. Peruski, 1997, *The Internet and the New Biology: Tools for Genomic and Molecular Research*, American Society for Microbiology, Washington, D.C.

Standard reference works setting forth the general principles of

immunology include S. Sell, 1996, *Immunology, Immunopathology & Immunity*, 5th Ed., Appleton & Lange, Publ., Stamford, CT; D. Male et al., 1996, *Advanced Immunology*, 3d Ed., Times Mirror Int'l Publishers Ltd., Publ., London; D.P. Stites and A.I. Terr, 1991, *Basic and Clinical Immunology*, 7th Ed., Appleton & Lange, Publ., Norwalk, CT; and A.K. Abbas et al., 1991, *Cellular and Molecular Immunology*, W. B. Saunders Co., Publ., Philadelphia, PA. Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention; however, preferred materials and/or methods are described. Materials, reagents, and the like to which reference is made in the following description and examples are generally obtainable from commercial sources, and specific vendors are cited herein.

#### **Nucleic Acids**

The present invention relates to isolated Gene 216 nucleic acids comprising genomic DNA within BAC RPCI\_1098L22 (e.g., SEQ ID NO:5), the corresponding cDNA sequences (e.g., SEQ ID NO:1 or SEQ ID NO:3), RNA, fragments of the genomic, cDNA, or RNA nucleic acids comprising at least 15, 20, 40, 60, 100, 200, 500, 1520, 2070, 3915, 5009, 6875, or more contiguous nucleotides, and the complements thereof. Closely related variants are also included as part of this invention, as well as nucleic acids sharing at least 50, 60, 70, 80, or 90% identity with the nucleic acids described above, and nucleic acids which would be identical to a Gene 216 nucleic acids except for one or a few substitutions, deletions, or additions.

The invention also relates to isolated nucleic acids comprising regions required for accurate expression of Gene 216 (e.g., Gene 216 promoter (e.g., SEQ ID NO:8), enhancer (e.g., SEQ ID NO:7), and polyadenylation sequences). In a preferred embodiment, the present invention is directed to at least 15 contiguous nucleotides of the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:6. More particularly, embodiments of this invention include the BAC clone containing segments of Gene 216 including RPCI\_1098L22 as set forth in SEQ ID NO:5 (Figure 7).

The invention further relates to nucleic acids (e.g., DNA or RNA) that

hybridize to a) a nucleic acid encoding a Gene 216 polypeptide, such as a nucleic acid having the sequence of SEQ ID NO:1 or SEQ ID NO:6; b) sequence-conservative, function-conservative, and non-conservative variants of (a); and c) fragments or portions of (a) or (b). Nucleic acids that hybridize to the sequence of SEQ ID NO:1 or SEQ ID NO:6 can be double- or single-stranded. Hybridization to the sequence of SEQ ID NO:1 or SEQ ID NO:6 includes hybridization to the strand shown or its complementary strand.

The present invention also relates to nucleic acids that encode a polypeptide having the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:363, or functional equivalents thereof. A functional equivalent of a Gene 216 protein includes fragments or variants that perform at least on characteristic function of the Gene 216 protein (e.g., proteolysis, adhesion, fusion, antigenic, or intracellular activity). Preferably, a functional equivalent will share at least 65% sequence identity with the Gene 216 polypeptide.

In preferred embodiments, nucleic acids of the present invention share at least 50%, preferably at least 60-70%, more preferably at least 70-80% sequence identity, and even more preferably at least 90-100% sequence identity with the sequences of SEQ ID NO:1 or SEQ ID NO:6, or fragments or portions thereof. Sequence identity calculations can be performed using computer programs, hybridization methods, or calculations. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, the GCG program package, BLASTN, BLASTX, TBLASTX, and FASTA (J. Devereux et al., 1984, *Nucleic Acids Research* **12**(1):387; S.F. Altschul et al., 1990, *J. Molec. Biol.* **215**:403-410; W. Gish and D.J. States, 1994, *Nature Genet.* **3**:266-272; W.R. Pearson and D.J. Lipman, 1988, *Proc Natl. Acad. Sci. USA* **85**(8):2444-8). The BLAST programs are publicly available from NCBI and other sources. The well-known Smith Waterman algorithm may also be used to determine identity.

For example, nucleotide sequence identity can be determined by comparing a query sequences to sequences in publicly available sequence databases (NCBI) using the BLASTN2 algorithm (S.F. Altschul et al., 1997,

*Nucl. Acids Res.*, **25**:3389-3402). The parameters for a typical search are:  $E = 0.05$ ,  $v = 50$ ,  $B = 50$ , wherein  $E$  is the expected probability score cutoff,  $V$  is the number of database entries returned in the reporting of the results, and  $B$  is the number of sequence alignments returned in the reporting of the results  
5 (S.F. Altschul et al., 1990, *J. Mol. Biol.*, **215**:403-410).

In another approach, nucleotide sequence identity can be calculated using the following equation:  $\% \text{ identity} = (\text{number of identical nucleotides}) / (\text{alignment length in nucleotides}) * 100$ . For this calculation, alignment length includes internal gaps but not includes terminal gaps. Alternatively, nucleotide  
10 sequence identity can be determined experimentally using the specific hybridization conditions described below.

In accordance with the present invention, polynucleotide alterations are selected from the group consisting of at least one nucleotide deletion, substitution, including transition and transversion, insertion, or modification  
15 (e.g., via RNA or DNA analogs). Alterations may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. Alterations of a polynucleotide sequence of SEQ ID NO:1 or SEQ  
20 ID NO:6 may create nonsense, missense, or frameshift mutations in this coding sequence, and thereby alter the polypeptide encoded by the polynucleotide following such alterations.

Such altered nucleic acids, including DNA or RNA, can be detected and isolated by hybridization under high stringency conditions or moderate  
25 stringency conditions, for example, which are chosen to prevent hybridization of nucleic acids having non-complementary sequences. "Stringency conditions" for hybridizations is a term of art which refers to the conditions of temperature and buffer concentration which permit hybridization of a particular nucleic acid to another nucleic acid in which the first nucleic acid may be  
30 perfectly complementary to the second, or the first and second may share some degree of complementarity which is less than perfect.

For example, certain high stringency conditions can be used which distinguish perfectly complementary nucleic acids from those of less complementarity. "High stringency conditions" and "moderate stringency conditions" for nucleic acid hybridizations are explained in F.M. Ausubel et al. (eds), 1995, *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc., New York, NY, the teachings of which are hereby incorporated by reference. In particular, see pages 2.10.1-2.10.16 (especially pages 2.10.8-2.10.11) and pages 6.3.1-6.3.6. The exact conditions which determine the stringency of hybridization depend not only on ionic strength, temperature and the concentration of destabilizing agents such as formamide, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences and the frequency of occurrence of subsets of that sequence within other non-identical sequences. Thus, high or moderate stringency conditions can be determined empirically.

By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions which will allow a given sequence to hybridize with the most similar sequences in the sample can be determined. Preferably the hybridizing sequences will have 60-70% sequence identity, more preferably 70-85% sequence identity, and even more preferably 90-100% sequence identity.

Typically, the hybridization reaction is initially performed under conditions of low stringency, followed by washes of varying, but higher stringency. Reference to hybridization stringency, e.g., high, moderate, or low stringency, typically relates to such washing conditions. Hybridization conditions are based on the melting temperature ( $T_m$ ) of the nucleic acid probe or primer and are typically classified by degree of stringency of the conditions under which hybridization is measured (Ausubel et al., 1995). For example, high stringency hybridization typically occurs at about 5-10% C below the  $T_m$ ; moderate stringency hybridization occurs at about 10-20% below the  $T_m$ ; and low stringency hybridization occurs at about 20-25% below the  $T_m$ . The melting temperature can be approximated by the formulas as known in the art,

depending on a number of parameters, such as the length of the hybrid or probe in number of nucleotides, or hybridization buffer ingredients and conditions. As a general guide,  $T_m$  decreases approximately 1°C with every 1% decrease in sequence identity at any given SSC concentration. Generally, 5 doubling the concentration of SSC results in an increase in  $T_m$  of ~17°C. Using these guidelines, the washing temperature can be determined empirically for moderate or low stringency, depending on the level of mismatch sought.

High stringency hybridization conditions are typically carried out at 65 to 68°C in 0.1 X SSC and 0.1% SDS. Highly stringent conditions allow 10 hybridization of nucleic acid molecules having about 95 to 100% sequence identity. Moderate stringency hybridization conditions are typically carried out at 50 to 65°C in 1 X SSC and 0.1% SDS. Moderate stringency conditions allow hybridization of sequences having at least about 80 to 95% nucleotide sequence identity. Low stringency hybridization conditions are typically carried 15 out at 40 to 50°C in 6 X SSC and 0.1% SDS. Low stringency hybridization conditions allow detection of specific hybridization of nucleic acid molecules having at least about 50 to 80% nucleotide sequence identity.

For example, high stringency conditions can be attained by hybridization in 50% formamide, 5 X Denhardt's solution, 5 X SSPE or SSC (1 X SSPE 20 buffer comprises 0.15 M NaCl, 10 mM  $\text{Na}_2\text{HPO}_4$ , 1 mM EDTA; 1 X SSC buffer comprises 150 mM NaCl, 15 mM sodium citrate, pH 7.0), 0.2% SDS at about 42°C, followed by washing in 1 X SSPE or SSC and 0.1% SDS at a temperature of at least about 42°C, preferably about 55°C, more preferably about 65°C. Moderate stringency conditions can be attained, for example, by 25 hybridization in 50% formamide, 5 X Denhardt's solution, 5 X SSPE or SSC, and 0.2% SDS at 42°C to about 50°C, followed by washing in 0.2 X SSPE or SSC and 0.2% SDS at a temperature of at least about 42°C, preferably about 55°C, more preferably about 65°C. Low stringency conditions can be attained, for example, by hybridization in 10% formamide, 5 X Denhardt's solution, 6 X 30 SSPE or SSC, and 0.2% SDS at 42°C, followed by washing in 1 X SSPE or SSC, and 0.2% SDS at a temperature of about 45°C, preferably about 50°C



in 4 X SSC at 60°C for 30 min.

High stringency hybridization procedures typically (1) employ low ionic strength and high temperature for washing, such as 0.015 M NaCl/ 0.0015 M sodium citrate, pH 7.0 (0.1 X SSC) with 0.1% sodium dodecyl sulfate (SDS) at 50°C; (2) employ during hybridization 50% (vol/vol) formamide with 5 X Denhardt's solution (0.1% weight/volume highly purified bovine serum albumin/0.1% wt/vol Ficoll/0.1% wt/vol polyvinylpyrrolidone), 50 mM sodium phosphate buffer at pH 6.5 and 5 X SSC at 42°C; or (3) employ hybridization with 50% formamide, 5 X SSC, 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 X Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 X SSC and 0.1% SDS.

In one particular embodiment, high stringency hybridization conditions may be attained by:

- 15       --       Prehybridization treatment of the support (e.g. nitrocellulose filter or nylon membrane), to which is bound the nucleic acid capable of hybridizing with any of the sequences of the invention, is carried out at 65°C for 6 hr with a solution having the following composition: 4 X SSC, 10 X Denhardt's (1 X Denhardt's comprises 1% Ficoll, 1% polyvinylpyrrolidone, 1% BSA (bovine serum albumin); 1 X SSC comprises of 0.15 M of NaCl and 0.015 M of sodium citrate, pH 7);
- 20       --       Replacement of the pre-hybridization solution in contact with the support by a buffer solution having the following composition: 4 X SSC, 1 X Denhardt's, 25 mM NaPO<sub>4</sub>, pH 7, 2 mM EDTA, 0.5% SDS, 100 µg/ml of sonicated salmon sperm DNA containing a nucleic acid derived from the sequences of the invention as probe, in particular a radioactive probe, and previously denatured by a treatment at 100°C for 3 min;
- 25       --       Incubation for 12 hr at 65°C;
- 30       --       Successive washings with the following solutions: 1) four washings with 2 X SSC, 1 X Denhardt's, 0.5% SDS for 45 min at 65°C; 2) two washings with 0.2 X SSC, 0.1 X SSC for 45 min at 65°C; and 3) 0.1 x SSC,

0.1% SDS for 45 min at 65°C.

Additional examples of high, medium, and low stringency conditions can be found in Sambrook et al., 1989. Exemplary conditions are also described in M.H. Krause and S.A. Aaronson, 1991, *Methods in Enzymology*, **200**:546-556; Ausubel et al., 1995. It is to be understood that the low, moderate and high stringency hybridization/washing conditions may be varied using a variety of ingredients, buffers, and temperatures well known to and practiced by the skilled practitioner.

Isolated nucleic acids that are characterized by their ability to hybridize to (a) a nucleic acid encoding a Gene 216 polypeptide, such as the nucleic acids depicted as SEQ ID NO:1 or SEQ ID NO:6, b) the complement of (a), (c) or a portion of (a) or (b) (e.g., under high or moderate stringency conditions), may further encode a protein or polypeptide having at least one function characteristic of a Gene 216 polypeptide, such as proteolysis, adhesion, fusion, and intracellular activity, or binding of antibodies that also bind to non-recombinant Gene 216 protein or polypeptide. The catalytic or binding function of a protein or polypeptide encoded by the hybridizing nucleic acid may be detected by standard enzymatic assays for activity or binding (e.g., assays that measure the binding of a transit peptide or a precursor, or other components of the translocation machinery). Enzymatic assays, complementation tests, or other suitable methods can also be used in procedures for the identification and/or isolation of nucleic acids which encode a polypeptide having the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:363, or a functional equivalent of this polypeptide. The antigenic properties of proteins or polypeptides encoded by hybridizing nucleic acids can be determined by immunological methods employing antibodies that bind to a Gene 216 polypeptide such as immunoblot, immunoprecipitation and radioimmunoassay. PCR methodology, including RAGE (Rapid Amplification of Genomic DNA Ends), can also be used to screen for and detect the presence of nucleic acids which encode Gene 216-like proteins and polypeptides, and to assist in cloning such nucleic acids from genomic DNA. PCR methods for these purposes can be found in M.A.

Innis et al., 1990, *PCR Protocols: A Guide to Methods and Applications*, Academic Press, Inc., San Diego, CA., incorporated herein by reference.

It is understood that, as a result of the degeneracy of the genetic code, many nucleic acid sequences are possible which encode a Gene 216-like protein or polypeptide. Some of these will share little identity to the nucleotide sequences of any known or naturally-occurring Gene 216-like gene but can be used to produce the proteins and polypeptides of this invention by selection of combinations of nucleotide triplets based on codon choices. Such variants, while not hybridizable to a naturally-occurring Gene 216 gene under conditions of high stringency, are contemplated within this invention.

Also encompassed by the present invention are alternate splice variants produced by differential processing of the primary transcript(s) from Gene 216 genomic DNA. An alternate splice variant may comprise, for example, the sequence of any one of SEQ ID NO:2 and SEQ ID NO:350-362. Alternate splice variants can also comprise other combinations of introns/exons of SEQ ID NO:1 or SEQ ID NO:6, which can be determined by those of skill in the art. Alternate splice variants can be determined experimentally, for example, by isolating and analyzing cellular RNAs (e.g., Southern blotting or PCR), or by screening cDNA libraries using the Gene 216 nucleic acid probes or primers described herein. In another approach, alternate splice variants can be predicted using various methods, computer programs, or computer systems available to practitioners in the field.

General methods for splice site prediction can be found in Nakata, 1985, *Nucleic Acids Res.* **13**:5327-5340. In addition, splice sites can be predicted using, for example, the GRAIL™ (E.C. Uberbacher and R.J. Mural, 1991, *Proc. Natl. Acad. Sci. USA*, **88**:11261-11265; E.C. Uberbacher, 1995, *Trends Biotech.*, **13**:497-500; available online at [hypertext transfer protocol grail.lsd.ornl.gov/grailexp](http://hypertexttransferprotocol.grail.lsd.ornl.gov/grailexp)); GenView (L. Milanese et al., 1993, *Proceedings of the Second International Conference on Bioinformatics, Supercomputing, and Complex Genome Analysis*, H.A. Lim et al. (eds), World Scientific Publishing, Singapore, pp. 573-588); SpliceView (Shapiro and Senapathy, 1987, *Nucleic*

*Acids Res.* **15**:7155-7174; Rogozin and Milanese, 1997, *J. Mol. Evol.* **45**:50-59; available online at the WebGene website at [hypertext transfer protocol on the world wide web at itba.mi.cnr.it/webgene](http://hypertexttransferprotocol.ontheworldwideweb.at/itba.mi.cnr.it/webgene)); and HSPL (V.V. Solovyev et al., 1994, *Nucleic Acids Res.* **22**:5156-5163; V.V. Solovyev et al., 1994, "The Prediction of Human Exons by Oligonucleotide Composition and Discriminant Analysis of Spliceable Open Reading Frames," R. Altman et al. (eds), *The Second International conference on Intelligent systems for Molecular Biology*, AAAI Press, Menlo Park, CA, pp. 354-362; V.V. Solovyev et al., 1993, "Identification Of Human Gene Functional Regions Based On Oligonucleotide Composition," L. Hunter et al. (eds), *In Proceedings of First International conference on Intelligent System for Molecular Biology*, Bethesda, pp. 371-379) computer systems.

Additionally, computer programs such as GeneParser (E.E. Snyder and G.D. Stormo, 1995, *J. Mol. Biol.* **248**: 1-18; E.E. Snyder and G.D. Stormo, 1993, *Nucl. Acids Res.* **21**(3): 607-613; available online at [hypertext transfer protocol mcdb.colorado.edu/~eesnyder/ GeneParser.html](http://hypertexttransferprotocol.mcdb.colorado.edu/~eesnyder/GeneParser.html)); MZEF (M.Q. Zhang, 1997, *Proc. Natl. Acad. Sci. USA*, **94**:565-568; available online at [hypertext transfer protocol argon.cshl.org/genefinder](http://hypertexttransferprotocol.argon.cshl.org/genefinder)); MORGAN (S. Salzberg et al., 1998, *J. Comp. Biol.* **5**:667-680; S. Salzberg et al. (eds), 1998, *Computational Methods in Molecular Biology*, Elsevier Science, New York, NY, pp. 187-203); VEIL (J. Henderson et al., 1997, *J. Comp. Biol.* **4**:127-141); GeneScan (S. Tiwari et al., 1997, *CABIOS (Bioinformatics)* **13**: 263-270); GeneBuilder (L. Milanese et al., 1999, *Bioinformatics* **15**:612-621); Eukaryotic GeneMark (J. Besemer et al., 1999, *Nucl. Acids Res.* **27**:3911-3920); and FEXH (V.V. Solovyev et al., 1994, *Nucleic Acids Res.* **22**:5156-5163). In addition, splice sites (i.e., former or potential splice sites) in cDNA sequences can be predicted using, for example, the RNASPL (V.V. Solovyev et al., 1994, *Nucleic Acids Res.* **22**:5156-5163); or INTRON (A. Globek et al., 1991, INTRON version 1.1 manual, Laboratory of Biochemical Genetics, NIMH, Washington, D.C.) programs.

The present invention also encompasses naturally-occurring

polymorphisms of Gene 216. As will be understood by those in the art, the genomes of all organisms undergo spontaneous mutation in the course of their continuing evolution generating variant forms of gene sequences (Gusella, 1986, *Ann. Rev. Biochem.* **55**:831-854). Restriction fragment length

5 polymorphisms (RFLPs) include variations in DNA sequences that alter the length of a restriction fragment in the sequence (Botstein et al., 1980, *Am. J. Hum. Genet.* **32**, 314-331 (1980). RFLPs have been widely used in human and animal genetic analyses (see WO 90/13668; WO90/11369; Donis-Keller, 1987, *Cell* **51**:319-337; Lander et al., 1989, *Genetics* **121**: 85-99). Short

10 tandem repeats (STRs) include tandem di-, tri- and tetranucleotide repeated motifs, also termed variable number tandem repeat (VNTR) polymorphisms. VNTRs have been used in identity and paternity analysis (U.S. Pat. No. 5,075,217; Armour et al., 1992, *FEBS Lett.* **307**:113-115; Horn et al., WO 91/14003; Jeffreys, EP 370,719), and in a large number of genetic mapping

15 studies.

Single nucleotide polymorphisms (SNPs) are far more frequent than RFLPs, STRs, and VNTRs. SNPs may occur in protein coding (e.g., exon), or non-coding (e.g., intron, 5'UTR, 3'UTR) sequences. SNPs in protein coding regions may comprise silent mutations that do not alter the amino acid

20 sequence of a protein. Alternatively, SNPs in protein coding regions may produce conservative or non-conservative amino acid changes, described in detail below. In some cases, SNPs may give rise to the expression of a defective or other variant protein and, potentially, a genetic disease. SNPs within protein-coding sequences can give rise to genetic diseases, for example,

25 in the  $\beta$ -globin (sickle cell anemia) and CFTR (cystic fibrosis) genes. In non-coding sequences, SNPs may also result in defective protein expression (e.g., as a result of defective splicing). Other single nucleotide polymorphisms have no phenotypic effects.

Single nucleotide polymorphisms can be used in the same manner as

30 RFLPs and VNTRs, but offer several advantages. Single nucleotide polymorphisms tend to occur with greater frequency and are typically spaced

more uniformly throughout the genome than other polymorphisms. Also, different SNPs are often easier to distinguish than other types of polymorphisms (e.g., by use of assays employing allele-specific hybridization probes or primers). In one embodiment of the present invention, a Gene 216  
5 nucleic acid contains at least one allele of one SNP as set forth in Table 10, herein below. Various combinations of these alleles (termed "haplotypes") are also encompassed by the invention. In a preferred aspect, a Gene 216 allele or haplotype is associated with a lung-related disorder, such as asthma.

The nucleic acid sequences of the present invention may be derived  
10 from a variety of sources including DNA, cDNA, synthetic DNA, synthetic RNA, or combinations thereof. Such sequences may comprise genomic DNA, which may or may not include naturally occurring introns. Moreover, such genomic DNA may be obtained in association with promoter regions or poly (A) sequences. The sequences, genomic DNA, or cDNA may be obtained in any  
15 of several ways. Genomic DNA can be extracted and purified from suitable cells by means well known in the art. Alternatively, mRNA can be isolated from a cell and used to produce cDNA by reverse transcription or other means.

The nucleic acids described herein are used in the methods of the present invention for production of proteins or polypeptides, through  
20 incorporation into cells, tissues, or organisms. In one embodiment, DNA containing all or part of the coding sequence for a Gene 216 polypeptide, or DNA which hybridizes to DNA having the sequence SEQ ID NO:1 or SEQ ID NO:6, is incorporated into a vector for expression of the encoded polypeptide in suitable host cells. The encoded polypeptide consisting of Gene 216, or its  
25 functional equivalent is capable of normal activity, such as proteolysis, adhesion, fusion, and intracellular activity.

The invention also concerns the use of the nucleotide sequence of the nucleic acids of this invention to identify DNA probes for Gene 216 genes, PCR primers to amplify Gene 216 genes, nucleotide polymorphisms in Gene 216  
30 genes, and regulatory elements of the Gene 216 genes.

The nucleic acids of the present invention find use as primers

and templates for the recombinant production of disorder-associated peptides or polypeptides, for chromosome and gene mapping, to provide antisense sequences, for tissue distribution studies, to locate and obtain full length genes, to identify and obtain homologous sequences (wild-type and mutants),  
5 and in diagnostic applications.

Probes may also be used for the detection of Gene 216-related sequences, and should preferably contain at least 50%, preferably at least 80%, identity to Gene 216 polynucleotide, or a complementary sequence, or fragments thereof. The probes of this invention may be DNA or RNA, the  
10 probes may comprise all or a portion of the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:6, or a complementary sequence thereof, and may include promoter, enhancer elements, and introns of the naturally occurring Gene 216 polynucleotide.

The probes and primers based on the Gene 216 gene sequences  
15 disclosed herein are used to identify homologous Gene 216 gene sequences and proteins in other species. These Gene 216 gene sequences and proteins are used in the diagnostic/prognostic, therapeutic and drug-screening methods described herein for the species from which they have been isolated.

#### **Vectors and Host Cells**

20 The invention also provides vectors comprising the disorder-associated sequences, or derivatives or fragments thereof, and host cells for the production of purified proteins. A large number of vectors, including bacterial, yeast, and mammalian vectors, have been described for replication and/or expression in various host cells or cell-free systems, and may be used  
25 for gene therapy as well as for simple cloning or protein expression.

In one aspect, an expression vectors comprises a nucleic acid encoding a Gene 216 polypeptide or peptide, as described herein, operably linked to at least one regulatory sequence. Regulatory sequences are known in the art and are selected to direct expression of the desired protein in an appropriate  
30 host cell. Accordingly, the term regulatory sequence includes promoters, enhancers and other expression control elements (see D.V. Goeddel (1990)

*Methods Enzymol.* **185**:3-7). Enhancer and other expression control sequences are described in *Enhancers and Eukaryotic Gene Expression*, Cold Spring Harbor Press, Cold Spring Harbor, NY (1983). It should be understood that the design of the expression vector may depend on such factors as the  
5 choice of the host cell to be transfected and/or the type of polypeptide desired to be expressed.

Several regulatory elements (e.g., promoters) have been isolated and shown to be effective in the transcription and translation of heterologous proteins in the various hosts. Such regulatory regions, methods of isolation,  
10 manner of manipulation, etc. are known in the art. Non-limiting examples of bacterial promoters include the  $\beta$ -lactamase (penicillinase) promoter; lactose promoter; tryptophan (trp) promoter; araBAD (arabinose) operon promoter; lambda-derived  $P_{\lambda}$  promoter and N gene ribosome binding site; and the hybrid tac promoter derived from sequences of the trp and lac UV5 promoters. Non-  
15 limiting examples of yeast promoters include the 3-phosphoglycerate kinase promoter, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) promoter, galactokinase (GAL1) promoter, galactose epimerase promoter, and alcohol dehydrogenase (ADH1) promoter. Suitable promoters for mammalian cells include, without limitation, viral promoters, such as those from Simian Virus  
20 (SV40), Rous sarcoma virus (RSV), adenovirus (ADV), and bovine papilloma virus (BPV). Preferred replication and inheritance systems include M13, ColE1, SV40, baculovirus, lambda, adenovirus, CEN ARS, 2 $\mu$ m ARS and the like. While expression vectors may replicate autonomously, they may also replicate by being inserted into the genome of the host cell, by methods well  
25 known in the art.

To obtain expression in eukaryotic cells, terminator sequences, polyadenylation sequences, and enhancer sequences that modulate gene expression may be required. Sequences that cause amplification of the gene may also be desirable. These sequences are well known in the art.  
30 Furthermore, sequences that facilitate secretion of the recombinant product from cells, including, but not limited to, bacteria, yeast, and animal cells, such



as secretory signal sequences and/or preprotein or proprotein sequences, may also be included. Such sequences are well described in the art.

Expression and cloning vectors will likely contain a selectable marker, a gene encoding a protein necessary for survival or growth of a host cell  
5 transformed with the vector. The presence of this gene ensures growth of only those host cells that express the inserts. Typical selection genes encode proteins that 1) confer resistance to antibiotics or other toxic substances, e.g. ampicillin, neomycin, methotrexate, etc.; 2) complement auxotrophic deficiencies, or 3) supply critical nutrients not available from complex media,  
10 e.g., the gene encoding D-alanine racemase for Bacilli. Markers may be an inducible or non-inducible gene and will generally allow for positive selection. Non-limiting examples of markers include the ampicillin resistance marker (i.e., beta-lactamase), tetracycline resistance marker, neomycin/kanamycin resistance marker (i.e., neomycin phosphotransferase), dihydrofolate  
15 reductase, glutamine synthetase, and the like. The choice of the proper selectable marker will depend on the host cell, and appropriate markers for different hosts as understood by those of skill in the art.

Suitable expression vectors for use with the present invention include, but are not limited to, pUC, pBluescript (Stratagene), pET (Novagen, Inc.,  
20 Madison, WI), and pREP (Invitrogen) plasmids. Vectors can contain one or more replication and inheritance systems for cloning or expression, one or more markers for selection in the host, e.g. antibiotic resistance, and one or more expression cassettes. The inserted coding sequences can be synthesized by standard methods, isolated from natural sources, or prepared  
25 as hybrids. Ligation of the coding sequences to transcriptional regulatory elements (e.g., promoters, enhancers, and/or insulators) and/or to other amino acid encoding sequences can be carried out using established methods.

Suitable cell-free expression systems for use with the present invention include, without limitation, rabbit reticulocyte lysate, wheat germ extract, canine  
30 pancreatic microsomal membranes, *E. coli* S30 extract, and coupled transcription/translation systems (Promega Corp., Madison, WI). These

systems allow the expression of recombinant polypeptides or peptides upon the addition of cloning vectors, DNA fragments, or RNA sequences containing protein-coding regions and appropriate promoter elements.

Non-limiting examples of suitable host cells include bacteria, archaea, insect, fungi (e.g., yeast), plant, and animal cells (e.g., mammalian, especially human). Of particular interest are *Escherichia coli*, *Bacillus subtilis*, *Saccharomyces cerevisiae*, SF9 cells, C129 cells, 293 cells, *Neurospora*, and immortalized mammalian myeloid and lymphoid cell lines. Techniques for the propagation of mammalian cells in culture are well-known (see, Jakoby and Pastan (eds), 1979, *Cell Culture. Methods in Enzymology*, volume 58, Academic Press, Inc., Harcourt Brace Jovanovich, NY). Examples of commonly used mammalian host cell lines are VERO and HeLa cells, CHO cells, and WI38, BHK, and COS cell lines, although it will be appreciated by the skilled practitioner that other cell lines may be used, e.g., to provide higher expression desirable glycosylation patterns, or other features.

Host cells can be transformed, transfected, or infected as appropriate by any suitable method including electroporation, calcium chloride-, lithium chloride-, lithium acetate/polyethylene glycol-, calcium phosphate-, DEAE-dextran-, liposome-mediated DNA uptake, spheroplasting, injection, microinjection, microprojectile bombardment, phage infection, viral infection, or other established methods. Alternatively, vectors containing the nucleic acids of interest can be transcribed *in vitro*, and the resulting RNA introduced into the host cell by well-known methods, e.g., by injection (see, Kubo et al., 1988, *FEBS Letts.* **241**:119). The cells into which have been introduced nucleic acids described above are meant to also include the progeny of such cells.

The nucleic acids of the invention may be isolated directly from cells. Alternatively, the polymerase chain reaction (PCR) method can be used to produce the nucleic acids of the invention, using either RNA (e.g., mRNA) or DNA (e.g., genomic DNA) as templates. Primers used for PCR can be synthesized using the sequence information provided herein and can further

be designed to introduce appropriate new restriction sites, if desirable, to facilitate incorporation into a given vector for recombinant expression.

Using the information provided in SEQ ID NO:1 and SEQ ID NO:6, one skilled in the art will be able to clone and sequence all representative nucleic acids of interest, including nucleic acids encoding complete protein-coding sequences. It is to be understood that non-protein-coding sequences contained within SEQ ID NO:1 and SEQ ID NO:3 and the genomic sequences of SEQ ID NO:6 and SEQ ID NO:5 are also within the scope of the invention. Such sequences include, without limitation, sequences important for replication, recombination, transcription, and translation. Non-limiting examples include promoters and regulatory binding sites involved in regulation of gene expression, and 5'- and 3'- untranslated sequences (e.g., ribosome-binding sites) that form part of mRNA molecules.

The nucleic acids of this invention can be produced in large quantities by replication in a suitable host cell. Natural or synthetic nucleic acid fragments, comprising at least ten contiguous bases coding for a desired peptide or polypeptide can be incorporated into recombinant nucleic acid constructs, usually DNA constructs, capable of introduction into and replication in a prokaryotic or eukaryotic cell. Usually the nucleic acid constructs will be suitable for replication in a unicellular host, such as yeast or bacteria, but may also be intended for introduction to (with and without integration within the genome) cultured mammalian or plant or other eukaryotic cells, cell lines, tissues, or organisms. The purification of nucleic acids produced by the methods of the present invention is described, for example, in Sambrook et al., 1989; F.M. Ausubel et al., 1992, *Current Protocols in Molecular Biology*, J. Wiley and Sons, New York, NY.

The nucleic acids of the present invention can also be produced by chemical synthesis, e.g., by the phosphoramidite method described by Beaucage et al., 1981, *Tetra. Letts.* **22**:1859-1862, or the triester method according to Matteucci et al., 1981, *J. Am. Chem. Soc.*, **103**:3185, and can be performed on commercial, automated oligonucleotide synthesizers. A double-

stranded fragment may be obtained from the single-stranded product of chemical synthesis either by synthesizing the complementary strand and annealing the strands together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer  
5 sequence.

These nucleic acids can encode full-length variant forms of proteins as well as the wild-type protein. The variant proteins (which could be especially useful for detection and treatment of disorders) will have the variant amino acid sequences encoded by the polymorphisms described in Table 10, when said  
10 polymorphisms are read so as to be in-frame with the full-length coding sequence of which it is a component.

Large quantities of the nucleic acids and proteins of the present invention may be prepared by expressing the Gene 216 nucleic acids or portions thereof in vectors or other expression vehicles in compatible  
15 prokaryotic or eukaryotic host cells. The most commonly used prokaryotic hosts are strains of *Escherichia coli*, although other prokaryotes, such as *Bacillus subtilis* or *Pseudomonas* may also be used. Mammalian or other eukaryotic host cells, such as those of yeast, filamentous fungi, plant, insect, or amphibian or avian species, may also be useful for production of the  
20 proteins of the present invention. For example, insect cell systems (i.e., lepidopteran host cells and baculovirus expression vectors) are particularly suited for large-scale protein production.

Host cells carrying an expression vector (i.e., transformants or clones) are selected using markers depending on the mode of the vector construction.  
25 The marker may be on the same or a different DNA molecule, preferably the same DNA molecule. In prokaryotic hosts, the transformant may be selected, e.g., by resistance to ampicillin, tetracycline or other antibiotics. Production of a particular product based on temperature sensitivity may also serve as an appropriate marker.

30 Prokaryotic or eukaryotic cells comprising the nucleic acids of the present invention will be useful not only for the production of the nucleic acids

and proteins of the present invention, but also, for example, in studying the characteristics of Gene 216 proteins. Cells and animals that carry the Gene 216 gene can be used as model systems to study and test for substances that have potential as therapeutic agents. The cells are typically cultured  
5 mesenchymal stem cells. These may be isolated from individuals with somatic or germline Gene 216 gene. Alternatively, the cell line can be engineered to carry the Gene 216 genes, as described above. After a test substance is applied to the cells, the transformed phenotype of the cell is determined. Any trait of transformed cells can be assessed, including respiratory diseases  
10 including asthma, atopy, and response to application of putative therapeutic agents.

#### **Antisense Nucleic Acids**

A further embodiment of the invention is antisense nucleic acids or oligonucleotides that are complementary, in whole or in part, to a target  
15 molecule comprising a sense strand of Gene 216. The Gene 216 target can be DNA, or its RNA counterpart (i.e., wherein thymine (T) is present in DNA and uracil (U) is present in RNA). When introduced into a cell, antisense nucleic acids or oligonucleotides can hybridize to all or a part of the sense strand of Gene 216, thereby inhibiting gene expression or replication.

20 In a particular embodiment of the invention, an antisense nucleic acid or oligonucleotide is wholly or partially complementary to, and can hybridize with, a target nucleic acid (either DNA or RNA) having the sequence of SEQ ID NO:1 or SEQ ID NO:6. For example, an antisense nucleic acid or oligonucleotide comprising 16 nucleotides can be sufficient to inhibit  
25 expression of the Gene 216 protein. Alternatively, an antisense nucleic acid or oligonucleotide can be complementary to 5' or 3' untranslated regions, or can overlap the translation initiation codon (5' untranslated and translated regions) of the Gene 216 gene, or its functional equivalent. In another embodiment, the antisense nucleic acid is wholly or partially complementary  
30 to, and can hybridize with, a target nucleic acid that encodes a Gene 216 polypeptide.

In addition, oligonucleotides can be constructed which will bind to duplex nucleic acid (i.e., DNA:DNA or DNA:RNA), to form a stable triple helix-containing or triplex nucleic acid. Such triplex oligonucleotides can inhibit transcription and/or expression of a gene encoding Gene 216, or its functional  
5 equivalent (M.D. Frank-Kamenetskii and S.M. Mirkin, 1995, *Ann. Rev. Biochem.* 64:65-95). Triplex oligonucleotides are constructed using the base-pairing rules of triple helix formation and the nucleotide sequence of the gene or mRNA for Gene 216.

The present invention encompasses methods of using oligonucleotides  
10 in antisense inhibition of the function of Gene 216. In the context of this invention, the term "oligonucleotide" refers to naturally-occurring species or synthetic species formed from naturally-occurring subunits or their close homologs. The term may also refer to moieties that function similarly to oligonucleotides, but have non-naturally-occurring portions. Thus,  
15 oligonucleotides may have altered sugar moieties or inter-sugar linkages. Exemplary among these are phosphorothioate and other sulfur containing species which are known in the art.

In preferred embodiments, at least one of the phosphodiester bonds of the oligonucleotide has been substituted with a structure that functions to  
20 enhance the ability of the compositions to penetrate into the region of cells where the RNA whose activity is to be modulated is located. It is preferred that such substitutions comprise phosphorothioate bonds, methyl phosphonate bonds, or short chain alkyl or cycloalkyl structures. In accordance with other preferred embodiments, the phosphodiester bonds are substituted with  
25 structures which are, at once, substantially non-ionic and non-chiral, or with structures which are chiral and enantiomerically specific. Persons of ordinary skill in the art will be able to select other linkages for use in the practice of the invention.

Oligonucleotides may also include species that include at least some  
30 modified base forms. Thus, purines and pyrimidines other than those normally found in nature may be so employed. Similarly, modifications on the furanosyl

portions of the nucleotide subunits may also be effected, as long as the essential tenets of this invention are adhered to. Examples of such modifications are 2'-O-alkyl- and 2'-halogen-substituted nucleotides. Some non-limiting examples of modifications at the 2' position of sugar moieties  
5 which are useful in the present invention include OH, SH, SCH<sub>3</sub>, F, OCH<sub>3</sub>, OCN, O(CH<sub>2</sub>)<sub>n</sub> NH<sub>2</sub> and O(CH<sub>2</sub>)<sub>n</sub> CH<sub>3</sub>, where n is from 1 to about 10. Such oligonucleotides are functionally interchangeable with natural oligonucleotides or synthesized oligonucleotides, which have one or more differences from the natural structure. All such analogs are comprehended by this invention so long  
10 as they function effectively to hybridize with Gene 216 DNA or RNA to inhibit the function thereof.

The oligonucleotides in accordance with this invention preferably comprise from about 3 to about 50 subunits. It is more preferred that such oligonucleotides and analogs comprise from about 8 to about 25 subunits and  
15 still more preferred to have from about 12 to about 20 subunits. As defined herein, a "subunit" is a base and sugar combination suitably bound to adjacent subunits through phosphodiester or other bonds.

Antisense nucleic acids or oligonucleotides can be produced by standard techniques (see, e.g., Shewmaker et al., U.S. Patent No. 5,107,065.  
20 The oligonucleotides used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is available from several vendors, including PE Applied Biosystems (Foster City, CA). Any other means for such synthesis may also be employed, however, the actual synthesis of the  
25 oligonucleotides is well within the abilities of the practitioner. It is also well known to prepare other oligonucleotide such as phosphorothioates and alkylated derivatives.

The oligonucleotides of this invention are designed to be hybridizable with Gene 216 RNA (e.g., mRNA) or DNA. For example, an oligonucleotide  
30 (e.g., DNA oligonucleotide) that hybridizes to Gene 216 mRNA can be used to target the mRNA for RNaseH digestion. Alternatively, an oligonucleotide that

hybridizes to the translation initiation site of Gene 216 mRNA can be used to prevent translation of the mRNA. In another approach, oligonucleotides that bind to the double-stranded DNA of Gene 216 can be administered. Such oligonucleotides can form a triplex construct and inhibit the transcription of the  
5 DNA encoding Gene 216 polypeptides. Triple helix pairing prevents the double helix from opening sufficiently to allow the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described (see, e.g., J.E. Gee et al., 1994, *Molecular and Immunologic Approaches*, Futura Publishing Co., Mt. Kisco, NY).

10 As non-limiting examples, antisense oligonucleotides may be targeted to hybridize to the following regions: mRNA cap region; translation initiation site; translational termination site; transcription initiation site; transcription termination site; polyadenylation signal; 3' untranslated region; 5' untranslated region; 5' coding region; mid coding region; and 3' coding region. Preferably,  
15 the complementary oligonucleotide is designed to hybridize to the most unique 5' sequence Gene 216, including any of about 15-35 nucleotides spanning the 5' coding sequence. Appropriate oligonucleotides can be designed using OLIGO software (Molecular Biology Insights, Inc., Cascade, CO; available online at hyperlink transfer protocol on the world wide web at oligo.net).

20 In accordance with the present invention, the antisense oligonucleotide can be synthesized, formulated as a pharmaceutical composition, and administered to a subject. The synthesis and utilization of antisense and triplex oligonucleotides have been previously described (e.g., H. Simon et al., 1999, *Antisense Nucleic Acid Drug Dev.* 9:527-31; F.X. Barre et al., 2000, *Proc. Natl. Acad. Sci. USA* 97:3084-3088; R. Elez et al., 2000, *Biochem. Biophys. Res. Commun.* 269:352-6; E.R. Sauter et al., 2000, *Clin. Cancer Res.* 6:654-60).  
25 Alternatively, expression vectors derived from retroviruses, adenovirus, herpes or vaccinia viruses, or from various bacterial plasmids may be used for delivery of nucleotide sequences to the targeted organ, tissue or cell population.  
30 Methods which are well known to those skilled in the art can be used to construct recombinant vectors which will express nucleic acid sequence that



is complementary to the nucleic acid sequence encoding a Gene 216 polypeptide. These techniques are described both in Sambrook et al., 1989 and in Ausubel et al., 1992. For example, Gene 216 expression can be inhibited by transforming a cell or tissue with an expression vector that  
5 expresses high levels of untranslatable sense or antisense Gene 216 sequences. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and even longer if appropriate replication elements included  
10 in the vector system.

Various assays may be used to test the ability of Gene 216-specific antisense oligonucleotides to inhibit Gene 216 expression. For example, Gene 216 mRNA levels can be assessed northern blot analysis (Sambrook et al., 1989; Ausubel et al., 1992; J.C. Alwine et al. 1977, *Proc. Natl. Acad. Sci. USA*  
15 **74**:5350-5354; I.M. Bird, 1998, *Methods Mol. Biol.* **105**:325-36), quantitative or semi-quantitative RT-PCR analysis (see, e.g., W.M. Freeman et al., 1999, *Biotechniques* **26**:112-122; Ren et al., 1998, *Mol. Brain Res.* **59**:256-63; J.M. Cale et al., 1998, *Methods Mol. Biol.* **105**:351-71), or *in situ* hybridization (reviewed by A.K. Raap, 1998, *Mutat. Res.* **400**:287-298). Alternatively,  
20 antisense oligonucleotides may be assessed by measuring levels of Gene 216 polypeptide, e.g., by western blot analysis, indirect immunofluorescence, immunoprecipitation techniques (see, e.g., J.M. Walker, 1998, *Protein Protocols on CD-ROM*, Humana Press, Totowa, NJ).

### **Polypeptides**

25 The invention also relates to polypeptides and peptides encoded by the novel nucleic acids described herein. The polypeptides and peptides of this invention can be isolated and/or recombinant. In a preferred embodiment, the Gene 216 polypeptide, or analog or portion thereof, has at least one function characteristic of a Gene 216 protein, for example, proteolysis, adhesion,  
30 fusion, antigenic, and intracellular activity. Protein analogs include, for example, naturally-occurring or genetically engineered Gene 216 variants (e.g.

mutants) and portions thereof. Variants may differ from wild-type Gene 216 protein by the addition, deletion, or substitution of one or more amino acid residues. In specific embodiments, polypeptide variants are encoded by Gene 216 nucleic acids containing one or more of the alleles or haplotypes disclosed  
 5 herein. Variants also include polypeptides in which one or more residues are modified (i.e., by phosphorylation, sulfation, acylation, etc.), and mutants comprising one or more modified residues.

Variant polypeptides can have conservative changes, wherein a substituted amino acid has similar structural or chemical properties, e.g.,  
 10 replacement of leucine with isoleucine. More infrequently, a variant polypeptide can have non-conservative changes, e.g., substitution of a glycine with a tryptophan. Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological or immunological activity can be found using computer programs well known in the art, for  
 15 example, DNASTAR software (DNASTAR, Inc., Madison, WI)

As non-limiting examples, conservative substitutions in the Gene 216 amino acid sequence can be made in accordance with the following table:

Original Residue	Conservative Substitution(s)
Ala	Ser
Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	Met, Leu, Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp, Phe
Val	Ile, Leu

Substantial changes in function or immunogenicity can be made by selecting substitutions that are less conservative than those shown in the table, above. For example, non-conservative substitutions can be made which more significantly affect the structure of the polypeptide in the area of the alteration, for example, the alpha-helical, or beta-sheet structure; the charge or hydrophobicity of the molecule at the target site; or the bulk of the side chain. The substitutions which generally are expected to produce the greatest changes in the polypeptide's properties are those where 1) a hydrophilic residue, e.g., seryl or threonyl, is substituted for (or by) a hydrophobic residue, e.g., leucyl, isoleucyl, phenylalanyl, valyl, or alanyl; 2) a cysteine or proline is substituted for (or by) any other residue; 3) a residue having an electropositive side chain, e.g., lysyl, arginyl, or histidyl, is substituted for (or by) an electronegative residue, e.g., glutamyl or aspartyl; or 4) a residue having a bulky side chain, e.g., phenylalanine, is substituted for (or by) a residue that does not have a side chain, e.g., glycine.

In one embodiment, polypeptides of the present invention share at least 50% amino acid sequence identity with a Gene 216 polypeptide, such as SEQ ID NO:4, or fragments thereof. Preferably, the polypeptides share at least 65% amino acid sequence identity; more preferably, the polypeptides share at least 75% amino acid sequence identity; even more preferably, the polypeptides share at least 80% amino acid sequence identity with a Gene 216 polypeptide; still more preferably the polypeptides share at least 90% amino acid sequence identity with a Gene 216 polypeptide.

Percent sequence identity can be calculated using computer programs or direct sequence comparison. Preferred computer program methods to determine identity between two sequences include, but are not limited to, the GCG program package, FASTA, BLASTP, and TBLASTN (see, e.g., D.W. Mount, 2001, *Bioinformatics: Sequence and Genome Analysis*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY). The BLASTP and TBLASTN programs are publicly available from NCBI and other sources. The

well-known Smith Waterman algorithm may also be used to determine identity.

Exemplary parameters for amino acid sequence comparison include the following: 1) algorithm from Needleman and Wunsch, 1970, *J Mol. Biol.* **48**:443-453; 2) BLOSSUM62 comparison matrix from Hentikoff and Hentikoff, 1992, *Proc. Natl. Acad. Sci. USA* **89**:10915-10919; 3) gap penalty = 12; and 4) gap length penalty = 4. A program useful with these parameters is publicly available as the "gap" program (Genetics Computer Group, Madison, WI). The aforementioned parameters are the default parameters for polypeptide comparisons (with no penalty for end gaps).

Alternatively, polypeptide sequence identity can be calculated using the following equation: % identity = (the number of identical residues) / (alignment length in amino acid residues) \* 100. For this calculation, alignment length includes internal gaps but does not include terminal gaps.

In accordance with the present invention, polypeptide sequences may be identical to the sequence of SEQ ID NO:4, or may include up to a certain integer number of amino acid alterations. Polypeptide alterations are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion. Alterations may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between those terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. In specific embodiments, polypeptide variants may be encoded by Gene 216 nucleic acids comprising SNP-related alleles or haplotypes and/or alternate splice variants.

The invention also relates to isolated, synthesized and/or recombinant portions or fragments of a Gene 216 protein or polypeptide as described herein. Polypeptide fragments (i.e., peptides) can be made which have full or partial function on their own, or which when mixed together (though fully, partially, or nonfunctional alone), spontaneously assemble with one or more other polypeptides to reconstitute a functional protein having at least one

functional characteristic of a Gene 216 protein of this invention. In addition, Gene 216 polypeptide fragments may comprise, for example, one or more domains of the Gene 216 polypeptide (e.g., the pre-, pro-, catalytic, cysteine-rich, disintegrin, EGF, transmembrane, and cytoplasmic domains) disclosed  
5 herein.

Polypeptides according to the invention can comprise at least 5 amino acid residues; preferably the polypeptides comprise at least 12 residues; more preferably the polypeptides comprise at least 20 residues; and yet more preferably the polypeptides comprise at least 30 residues. Nucleic acids  
10 comprising protein-coding sequences can be used to direct the expression of asthma-associated polypeptides in intact cells or in cell-free translation systems. The coding sequence can be tailored, if desired, for more efficient expression in a given host organism, and can be used to synthesize oligonucleotides encoding the desired amino acid sequences. The resulting  
15 oligonucleotides can be inserted into an appropriate vector and expressed in a compatible host organism or translation system.

The polypeptides of the present invention, including function-conservative variants, may be isolated from wild-type or mutant cells (e.g., human cells or cell lines), from heterologous organisms or cells (e.g., bacteria,  
20 yeast, insect, plant, and mammalian cells), or from cell-free translation systems (e.g., wheat germ, microsomal membrane, or bacterial extracts) in which a protein-coding sequence has been introduced and expressed. Furthermore, the polypeptides may be part of recombinant fusion proteins. The polypeptides can also, advantageously, be made by synthetic chemistry. Polypeptides may  
25 be chemically synthesized by commercially available automated procedures, including, without limitation, exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis.

Methods for polypeptide purification are well-known in the art, including, without limitation, preparative disc-gel electrophoresis, isoelectric focusing,  
30 HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. For some purposes, it is

preferable to produce the polypeptide in a recombinant system in which the protein contains an additional sequence (e.g., epitope or protein) tag that facilitates purification. Non-limiting examples of epitope tags include c-myc, haemagglutinin (HA), polyhistidine (6X-HIS) (SEQ ID NO:32), GLU-GLU, and  
5 DYKDDDDK (SEQ ID NO:33) (FLAG®) epitope tags. Non-limiting examples of protein tags include glutathione-S-transferase (GST), green fluorescent protein (GFP), and maltose binding protein (MBP).

In one approach, the coding sequence of a polypeptide or peptide can be cloned into a vector that creates a fusion with a sequence tag of interest.  
10 Suitable vectors include, without limitation, pRSET (Invitrogen Corp., San Diego, CA), pGEX (Amersham-Pharmacia Biotech, Inc., Piscataway, NJ), pEGFP (CLONTECH Laboratories, Inc., Palo Alto, CA), and pMAL™ (New England BioLabs (NEB), Inc., Beverly, MA) plasmids. Following expression, the epitope, or protein tagged polypeptide or peptide can be purified from a  
15 crude lysate of the translation system or host cell by chromatography on an appropriate solid-phase matrix. In some cases, it may be preferable to remove the epitope or protein tag (i.e., via protease cleavage) following purification. As an alternative approach, antibodies produced against a disorder-associated protein or against peptides derived therefrom can be used as purification  
20 reagents. Other purification methods are possible.

The present invention also encompasses polypeptide derivatives of Gene 216. The isolated polypeptides may be modified by, for example, phosphorylation, sulfation, acylation, or other protein modifications. They may also be modified with a label capable of providing a detectable signal, either  
25 directly or indirectly, including, but not limited to, radioisotopes and fluorescent compounds.

Both the naturally occurring and recombinant forms of the polypeptides of the invention can advantageously be used to screen compounds for binding activity. Many methods of screening for binding activity are known by those  
30 skilled in the art and may be used to practice the invention. Several methods of automated assays have been developed in recent years so as to permit

screening of tens of thousands of compounds in a short period of time. Such high-throughput screening methods are particularly preferred. The use of high-throughput screening assays to test for inhibitors is greatly facilitated by the availability of large amounts of purified polypeptides, as provided by the invention. The polypeptides of the invention also find use as therapeutic agents as well as antigenic components to prepare antibodies.

The polypeptides of this invention find use as immunogenic components useful as antigens for preparing antibodies by standard methods. It is well known in the art that immunogenic epitopes generally contain at least about five amino acid residues (Ohno et al., 1985, *Proc. Natl. Acad. Sci. USA* 82:2945). Therefore, the immunogenic components of this invention will typically comprise at least 5 amino acid residues of the sequence of the complete polypeptide chains. Preferably, they will contain at least 7, and most preferably at least about 10 amino acid residues or more to ensure that they will be immunogenic. Whether a given component is immunogenic can readily be determined by routine experimentation. Such immunogenic components can be produced by proteolytic cleavage of larger polypeptides or by chemical synthesis or recombinant technology and are thus not limited by proteolytic cleavage sites. The present invention thus encompasses antibodies that specifically recognize asthma-associated immunogenic components.

### **Structural Studies**

A purified Gene 216 polypeptide can be analyzed by well-established methods (e.g., X-ray crystallography, NMR, CD, etc.) to determine the three-dimensional structure of the molecule. The three-dimensional structure, in turn, can be used to model intermolecular interactions. Exemplary methods for crystallization and X-ray crystallography are found in P.G. Jones, 1981, *Chemistry in Britain*, 17:222-225; C. Jones et al. (eds), *Crystallographic Methods and Protocols*, Humana Press, Totowa, NJ; A. McPherson, 1982, *Preparation and Analysis of Protein Crystals*, John Wiley & Sons, New York, NY; T.L. Blundell and L.N. Johnson, 1976, *Protein Crystallography*, Academic Press, Inc., New York, NY; A. Holden and P. Singer, 1960, *Crystals and Crystal*

*Growing*, Anchor Books-Doubleday, New York, NY; R.A. Laudise, 1970, *The Growth of Single Crystals*, Solid State Physical Electronics Series, N. Holonyak, Jr., (ed), Prentice-Hall, Inc.; G.H. Stout and L.H. Jensen, 1989, *X-ray Structure Determination: A Practical Guide*, 2nd edition, John Wiley & Sons, New York, NY; *Fundamentals of Analytical Chemistry*, 3rd. edition, Saunders Golden Sunburst Series, Holt, Rinehart and Winston, Philadelphia, PA, 1976; P.D. Boyle of the Department of Chemistry of North Carolina State University website at [hypertext transfer protocol laue.chem.ncsu.edu/web/GrowXtal.html](http://hypertext.transfer.protocol.laue.chem.ncsu.edu/web/GrowXtal.html); M.B. Berry, 1995, *Protein Crystalization: Theory and Practice, Structure and Dynamics of E. coli Adenylate Kinase*, Doctoral Thesis, Rice University, Houston TX.

For X-ray diffraction studies, single crystals can be grown to suitable size. Preferably, a crystal has a size of 0.2 to 0.4 mm in at least two of the three dimensions. Crystals can be formed in a solution comprising a Gene 216 polypeptide (e.g., 1.5-200 mg/ml) and reagents that reduce the solubility to conditions close to spontaneous precipitation. Factors that affect the formation of polypeptide crystals include: 1) purity; 2) substrates or co-factors; 3) pH; 4) temperature; 5) polypeptide concentration; and 6) characteristics of the precipitant. Preferably, the Gene 216 polypeptides are pure, i.e., free from contaminating components (at least 95% pure), and free from denatured Gene 216 polypeptides. In particular, polypeptides can be purified by FPLC and HPLC techniques to assure homogeneity (see, Lin et al., 1992, *J. Crystal. Growth*. **122**:242-245). Optionally, Gene 216 polypeptide substrates or co-factors can be added to stabilize the quaternary structure of the protein and promote lattice packing.

Suitable precipitants for crystallization include, but are not limited to, salts (e.g., ammonium sulphate, potassium phosphate); polymers (e.g., polyethylene glycol (PEG) 6000); alcohols (e.g., ethanol); polyalcohols (e.g., 1-methyl-2,4 pentane diol (MPD)); organic solvents; sulfonic dyes; and deionized water. The ability of a salt to precipitate polypeptides can be generally described by the Hofmeister series:  $\text{PO}_4^{3-} > \text{HPO}_4^{2-} = \text{SO}_4^{2-} > \text{citrate}$



>  $\text{CH}_3\text{CO}_2^-$  >  $\text{Cl}^-$  >  $\text{Br}^-$  >  $\text{NO}_3^-$  >  $\text{ClO}_4^-$  >  $\text{SCN}^-$ ; and  $\text{NH}_4^+$  >  $\text{K}^+$  >  $\text{Na}^+$  >  $\text{Li}^+$ . Non-limiting examples of salt precipitants are shown below (see Berry, 1995).

Precipitant	Maximum concentration
$(\text{NH}_4^+/\text{Na}^+/\text{Li}^+)_2$ or $\text{Mg}_2+\text{SO}_4^{2-}$	4.0 / 1.5 / 2.1 / 2.5 M
$\text{NH}_4^+/\text{Na}^+/\text{K}^+ \text{PO}_4^{3-}$	3.0 / 4.0 / 4.0 M
$\text{NH}_4^+/\text{K}^+/\text{Na}^+/\text{Li}^+$ citrate	~1.8 M
$\text{NH}_4^+/\text{K}^+/\text{Na}^+/\text{Li}^+$ acetate	~3.0 M
$\text{NH}_4^+/\text{K}^+/\text{Na}^+/\text{Li}^+ \text{Cl}^-$	5.2 / 9.8 / 4.2 / 5.4 M
$\text{NH}_4^+ \text{NO}_3^-$	~8.0 M

- 5 High molecular weight polymers useful as precipitating agents include polyethylene glycol (PEG), dextran, polyvinyl alcohol, and polyvinyl pyrrolidone (A. Polson et al., 1964, *Biochem. Biophys. Acta.* **82**:463-475). In general, polyethylene glycol (PEG) is the most effective for forming crystals. PEG compounds with molecular weights less than 1000 can be used at concentrations above 40% v/v. PEGs with molecular weights above 1000 can be used at concentration 5-50% w/v. Typically, PEG solutions are mixed with ~0.1 % sodium azide to prevent bacterial growth.

- Typically, crystallization requires the addition of buffers and a specific salt content to maintain the proper pH and ionic strength for a protein's stability.
- 15 Suitable additives include, but are not limited to sodium chloride (e.g., 50-500 mM as additive to PEG and MPD; 0.15-2 M as additive to PEG); potassium chloride (e.g., 0.05-2 M); lithium chloride (e.g., 0.05-2 M); sodium fluoride (e.g., 20-300 mM); ammonium sulfate (e.g., 20-300 mM); lithium sulfate (e.g., 0.05-2 M); sodium or ammonium thiocyanate (e.g., 50-500 mM); MPD (e.g., 0.5-50%);
- 20 1,6 hexane diol (e.g., 0.5-10%); 1,2,3 heptane triol (e.g., 0.5-15%); and benzamidine (e.g., 0.5-15%).

- Detergents may be used to maintain protein solubility and prevent aggregation. Suitable detergents include, but are not limited to non-ionic detergents such as sugar derivatives, oligoethyleneglycol derivatives,
- 25 dimethylamine-N-oxides, cholate derivatives, N-octyl hydroxyalkylsulphoxides, sulphobetains, and lipid-like detergents. Sugar-derived detergents include alkyl glucopyranosides (e.g., C8-GP, C9-GP), alkyl thio-glucopyranosides (e.g., C8-

tGP), alkyl maltopyranosides (e.g., C10-M, C12-M; CYMAL-3, CYMAL-5, CYMAL-6), alkyl thio-maltopyranosides, alkyl galactopyranosides, alkyl sucroses (e.g., N-octanoylsucrose), and glucamides (e.g., HECAMEG, C-HEGA-10; MEGA-8). Oligoethyleneglycol-derived detergents include alkyl  
5 polyoxyethylenes (e.g., C8-E5, C8-En; C12-E8; C12-E9) and phenyl polyoxyethylenes (e.g., Triton X-100). Dimethylamine-N-oxide detergents include, e.g., C10-DAO; DDAO; LDAO. Cholate-derived detergents include, e.g., Deoxy-Big CHAP, digitonin. Lipid-like detergents include phosphocholine compounds. Suitable detergents further include zwitter-ionic detergents (e.g.,  
10 ZWITTERGENT 3-10; ZWITTERGENT 3-12); and ionic detergents (e.g., SDS).

Crystallization of macromolecules has been performed at temperatures ranging from 60°C to less than 0°C. However, most molecules can be crystallized at 4°C or 22°C. Lower temperatures promote stabilization of polypeptides and inhibit bacterial growth. In general, polypeptides are more  
15 soluble in salt solutions at lower temperatures (e.g., 4°C), but less soluble in PEG and MPD solutions at lower temperatures. To allow crystallization at 4°C or 22°C, the precipitant or protein concentration can be increased or decreased as required. Heating, melting, and cooling of crystals or aggregates can be used to enlarge crystals. In addition, crystallization at both 4°C and 22°C can  
20 be assessed (A. McPherson, 1992, *J. Cryst. Growth.* **122**:161-167; C.W. Carter, Jr. and C.W. Carter, 1979, *J. Biol. Chem.* **254**:12219-12223; T. Bergfors, 1993, *Crystallization Lab Manual*).

A crystallization protocol can be adapted to a particular polypeptide or peptide. In particular, the physical and chemical properties of the polypeptide  
25 can be considered (e.g., aggregation, stability, adherence to membranes or tubing, internal disulfide linkages, surface cysteines, chelating ions, etc.). For initial experiments, the standard set of crystallization reagents can be used (Hampton Research, Laguna Niguel, CA). In addition, the CRYSTOOL program can provide guidance in determining optimal crystallization conditions  
30 (Brent Segelke, 1995, *Efficiency analysis of sampling protocols used in protein crystallization screening and crystal structure from two novel crystal forms of*

PLA2, Ph.D. Thesis, University of California, San Diego). Exemplary crystallization conditions are shown below (see Berry, 1995).

Major Precipitant	Additive	Concentration of Major Precipitant	Concentration of Additive
(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub>	PEG 400-2000, MPD, ethanol, or methanol	2.0-4.0 M	6%-0.5%
Na citrate	PEG 400-2000, MPD, ethanol, or methanol	1.4-1.8 M	6%-0.5%
PEG 1000-20000	(NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub> , NaCl, or Na formate	40-50%	0.2-0.6 M

5 Robots can be used for automatic screening and optimization of crystallization conditions. For example, the IMPAX and Oryx systems can be used (Douglas Instruments, Ltd., East Garston, United Kingdom). The CRYSTOOL program (Segelke, *supra*) can be integrated with the robotics programming. In addition, the Xact program can be used to construct,  
 10 maintain, and record the results of various crystallization experiments (see, e.g., D.E. Brodersen et al., 1999, *J. Appl. Cryst.* **32**: 1012-1016; G.R. Andersen and J. Nyborg, 1996, *J. Appl. Cryst.* **29**:236-240). The Xact program supports multiple users and organizes the results of crystallization experiments into hierarchies. Advantageously, Xact is compatible with both CRYSTOOL and  
 15 Microsoft® Excel programs.

Four methods are commonly employed to crystallize macromolecules: vapor diffusion, free interface diffusion, batch, and dialysis. The vapor diffusion technique is typically performed by formulating a 1:1 mixture of a solution comprising the polypeptide of interest and a solution containing the  
 20 precipitant at the final concentration that is to be achieved after vapor equilibration. The drop containing the 1:1 mixture of protein and precipitant is then suspended and sealed over the well solution, which contains the precipitant at the target concentration, as either a hanging or sitting drop. Vapor diffusion can be used to screen a large number of crystallization  
 25 conditions or when small amounts of polypeptide are available. For screening, drop sizes of 1 to 2  $\mu$ l can be used. Once preliminary crystallization conditions have been determined, drop sizes such as 10  $\mu$ l can be used. Notably, results

from hanging drops may be improved with agarose gels (see K. Provost and M.-C. Robert, 1991, *J. Cryst. Growth*. **110**:258-264).

Free interface diffusion is performed by layering of a low density solution onto one of higher density, usually in the form of concentrated protein  
5 onto concentrated salt. Since the solute to be crystallized must be concentrated, this method typically requires relatively large amounts of protein. However, the method can be adapted to work with small amounts of protein. In a representative experiment, 2 to 5  $\mu$ l of sample is pipetted into one end of a 20  $\mu$ l microcapillary pipet. Next, 2 to 5  $\mu$ l of precipitant is pipetted into the  
10 capillary without introducing an air bubble, and the ends of the pipet are sealed. With sufficient amounts of protein, this method can be used to obtain relatively large crystals (see, e.g., S.M. Althoff et al., 1988, *J. Mol. Biol.* **199**:665-666).

The batch technique is performed by mixing concentrated polypeptide  
15 with concentrated precipitant to produce a final concentration that is supersaturated for the solute macromolecule. Notably, this method can employ relatively large amounts of solution (e.g., milliliter quantities), and can produce large crystals. For that reason, the batch technique is not recommended for screening initial crystallization conditions.

20 The dialysis technique is performed by diffusing precipitant molecules through a semipermeable membrane to slowly increase the concentration of the solute inside the membrane. Dialysis tubing can be used to dialyze milliliter quantities of sample, whereas dialysis buttons can be used to dialyze microliter quantities (e.g., 7-200  $\mu$ l). Dialysis buttons may be constructed out of glass,  
25 perspex, or Teflon™ (see, e.g., Cambridge Repetition Engineers Ltd., Greens Road, Cambridge CB4 3EQ, UK; Hampton Research). Using this method, the precipitating solution can be varied by moving the entire dialysis button or sack into a different solution. In this way, polypeptides can be "reused" until the correct conditions for crystallization are found (see, e.g., C.W. Carter, Jr. et al.,  
30 1988, *J. Cryst. Growth*. **90**:60-73). However, this method is not recommended for precipitants comprising concentrated PEG solutions.

Various strategies have been designed to screen crystallization conditions, including 1) pI screening; 2) grid screening; 3) factorials; 4) solubility assays; 5) perturbation; and 6) sparse matrices. In accordance with the pI screening method, the pI of a polypeptide is presumed to be its  
5 crystallization point. Screening at the pI can be performed by dialysis against low concentrations of buffer (less than 20 mM) at the appropriate pH, or by use of conventional precipitants.

The grid screening method can be performed on two-dimensional matrices. Typically, the precipitant concentration is plotted against pH. The  
10 optimal conditions can be determined for each axis, and then combined. At that point, additional factors can be tested (e.g., temperature, additives). This method works best with fast-forming crystals, and can be readily automated (see M.J. Cox and P.C. Weber, 1988, *J. Cryst. Growth*. **90**:318-324). Grid screens are commercially available for popular precipitants such as ammonium  
15 sulphate, PEG 6000, MPD, PEG/LiCl, and NaCl (see, e.g., Hamilton Research).

The incomplete factorial method can be performed by 1) selecting a set of ~20 conditions; 2) randomly assigning combinations of these conditions; 3) grading the success of the results of each experiment using an objective scale;  
20 and 4) statistically evaluating the effects of each of the conditions on crystal formation (see, e.g., C.W. Carter, Jr. et al., 1988, *J. Cryst. Growth*. **90**:60-73). In particular, conditions such as pH, temperature, precipitating agent, and cations can be tested. Dialysis buttons are preferably used with this method. Typically, optimal conditions/combinations can be determined within 35 tests.  
25 Similar approaches, such as "footprinting" conditions, may also be employed (see, e.g., E.A. Stura et al., 1991, *J. Cryst. Growth*. **110**:1-2).

The perturbation approach can be performed by altering crystallization conditions by introducing a series of additives designed to test the effects of altering the structure of bulk solvent and the solvent dielectric on crystal  
30 formation (see, e.g., Whitaker et al., 1995, *Biochem.* **34**:8221-8226). Additives for increasing the solvent dielectric include, but are not limited to, NaCl, KCl,

or LiCl (e.g., 200 mM); Na formate (e.g., 200 mM); Na<sub>2</sub>HPO<sub>4</sub> or K<sub>2</sub>HPO<sub>4</sub> (e.g., 200 mM); urea, trichloroacetate, guanidium HCl, or KSCN (e.g., 20-50 mM).

A non-limiting list of additives for decreasing the solvent dielectric include methanol, ethanol, isopropanol, or tert-butanol (e.g., 1-5%); MPD (e.g., 1%);

- 5 PEG 400, PEG 600, or PEG 1000 (e.g., 1-4%); PEG MME (monomethylether) 550, PEG MME 750, PEG MME 2000 (e.g., 1-4%).

As an alternative to the above-screening methods, the sparse matrix approach can be used (see, e.g., J. Jancarik and S.-H.J. Kim, 1991, *Appl. Cryst.* **24**:409-411; A. McPherson, 1992, *J. Cryst. Growth.* **122**:161-167; B.

- 10 Cudney et al., 1994, *Acta. Cryst.* **D50**:414-423). Sparse matrix screens are commercially available (see, e.g., Hampton Research; Molecular Dimensions, Inc., Apopka, FL; Emerald Biostructures, Inc., Lemont, IL). Notably, data from Hampton Research sparse matrix screens can be stored and analyzed using ASPRUN software (Douglas Instruments).

- 15 Exemplary conditions for an initial screen are shown below (see Berry, 1995).

**TABLE 1**

**Tray 1:**

PEG 8000 (wells 1-6)						Ammonium sulfate (wells 7-12)					
1	2	3	4	5	6	7	8	9	10	11	12
20%	20%	20%	35%	35%	35%	2.0 M	2.0 M	2.0 M	2.5 M	2.5 M	2.5 M
pH 5.0	pH 7.0	pH 8.8	pH 5.0	pH 7.0	pH 8.8	pH 5.0	pH 7.0	pH 8.8	pH 5.0	pH 7.0	pH 8.8
MPD (wells 13-16)				Na Citrate (wells 17-20)				Na/K Phosphate (wells 21-24)			
13	14	15	16	17	18	19	20	21	22	23	24
30%	30%	50%	50%	1.3 M	1.3 M	1.5 M	1.5 M	2.0 M	2.0 M	2.5 M	2.5 M
pH 5.8	pH 7.6	pH 5.8	pH 7.6	pH 5.8	pH 7.5	pH 5.8	pH 7.5	pH 6.0	pH 7.4	pH 6.0	pH 7.4

- 20 **Tray 2:**

PEG 2000 MME/0.2 M Ammon. sulfate (wells 25-30)					
25	26	27	28	29	30
25%	25%	25%	40%	40%	40%
pH 5.5	pH 7.0	pH 8.5	pH 5.5	pH 7.0	pH 8.5
Random for wells 31 to 48					

The initial screen can be used with hanging or sitting drops. To conserve the sample, tray 2 can be set up several weeks following tray 1.

- 25 Wells 31-48 of tray 2 can comprise a random set of solutions. Alternatively, solutions can be formulated using sparse methods. Preferably, test solutions cover a broad range of precipitants, additives, and pH (especially pH 5.0-9.0).

Seeding can be used to trigger nucleation and crystal growth (Stura and

Wilson, 1990, *J. Cryst. Growth*. 110:270-282; C. Thaller et al., 1981, *J. Mol. Biol.* 147:465-469; A. McPherson and P. Schlichta, 1988, *J. Cryst. Growth*. 90:47-50). In general, seeding can be performed by transferring crystal seeds into a polypeptide solution to allow polypeptide molecules to deposit on the surface of the seeds and produce crystals. Two seeding methods can be used: microseeding and macroseeding. For microseeding, a crystal can be ground into tiny pieces and transferred into the protein solution. Alternatively, seeds can be transferred by adding 1-2  $\mu$ l of the seed solution directly to the equilibrated protein solution. In another approach, seeds can be transferred by dipping a hair in the seed solution and then streaking the hair across the surface of the drop (streak seeding; see Stura and Wilson, *supra*). For macroseeding, an intact crystal can be transferred into the protein solution (see, e.g., C. Thaller et al., 1981, *J. Mol. Biol.* 147:465-469). Preferably, the surface of the crystal seed is washed to regenerate the growing surface prior to being transferred. Optimally, the protein solution for crystallization is close to saturation and the crystal seed is not completely dissolved upon transfer.

### **Antibodies**

An isolated Gene 216 polypeptide or a portion or fragment thereof, can be used as an immunogen to generate anti-Gene 216 antibodies using standard techniques for polyclonal and monoclonal antibody preparation. The full-length Gene 216 polypeptide can be used or, alternatively, the invention provides antigenic peptide fragments of Gene 216 for use as immunogens. The antigenic peptide of Gene 216 comprises at least 5 amino acid residues of the amino acid sequence shown in SEQ ID NO:4, and encompasses an epitope of Gene 216 such that an antibody raised against the peptide forms a specific immune complex with Gene 216 amino acid sequence.

Accordingly, another aspect of the invention pertains to anti-Gene 216 antibodies. The invention provides polyclonal and monoclonal antibodies that bind Gene 216 polypeptides or peptides. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site

capable of immunoreacting with a particular epitope of a Gene 216 polypeptide or peptide. A monoclonal antibody composition thus typically displays a single binding affinity for a particular Gene 216 polypeptide or peptide with which it immunoreacts.

5           A Gene 216 immunogen typically is used to prepare antibodies by immunizing a suitable subject, (e.g., rabbit, goat, mouse, or other non-human mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed Gene 216 polypeptide or a chemically synthesized Gene 216 polypeptide, or fragments thereof. The  
10       preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an immunogenic Gene 216 preparation induces a polyclonal anti-Gene 216 antibody response.

          A number of adjuvants are known and used by those skilled in the art.  
15       Non-limiting examples of suitable adjuvants include incomplete Freund's adjuvant, mineral gels such as alum, aluminum phosphate, aluminum hydroxide, aluminum silica, and surface-active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol. Further examples of adjuvants include N-  
20       acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-nor-muramyl-L-alanyl-D-isoglutamine (CGP 11637, referred to as nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3  
      hydroxyphosphoryloxy)-ethylamine (CGP 19835A, referred to as MTP-PE), and RIBI, which contains three components extracted from bacteria,  
25       monophosphoryl lipid A, trehalose dimycolate and cell wall skeleton (MPL+TDM+CWS) in a 2% squalene/Tween 80 emulsion. A particularly useful adjuvant comprises 5% (wt/vol) squalene, 2.5% Pluronic L121 polymer and 0.2% polysorbate in phosphate buffered saline (Kwak et al., 1992, *New Eng. J. Med.* **327**:1209-1215). Preferred adjuvants include complete BCG, Detox,  
30       (RIBI, Immunochem Research Inc.), ISCOMS, and aluminum hydroxide adjuvant (Superphos, Biosector). The effectiveness of an adjuvant may be



determined by measuring the amount of antibodies directed against the immunogenic peptide.

Polyclonal anti-Gene 216 antibodies can be prepared as described above by immunizing a suitable subject with a Gene 216 immunogen. The anti-Gene 216 antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized Gene 216. If desired, the antibody molecules directed against Gene 216 can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction.

At an appropriate time after immunization, e.g., when the anti-Gene 216 antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique (see Kohler and Milstein, 1975, *Nature* **256**:495-497; Brown et al., 1981, *J. Immunol.* **127**:539-46; Brown et al., 1980, *J. Biol. Chem.* **255**:4980-83; Yeh et al., 1976, *PNAS* **76**:2927-31; and Yeh et al., 1982, *Int. J. Cancer* **29**:269-75), the human B cell hybridoma technique (Kozbor et al., 1983, *Immunol. Today* **4**:72), the EBV-hybridoma technique (Cole et al., 1985, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques.

The technology for producing hybridomas is well-known (see generally R. H. Kenneth, 1980, *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, NY; E.A. Lerner, 1981, *Yale J. Biol. Med.*, **54**:387-402; M.L. Geffer et al., 1977, *Somatic Cell Genet.* **3**:231-36). In general, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a Gene 216 immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds Gene 216 polypeptides or peptides.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-

Gene 216 monoclonal antibody (see, e.g., G. Galfre et al., 1977, *Nature* **266**:55052; Gefter et al., 1977; Lerner, 1981; Kenneth, 1980). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods. Typically, the immortal cell line (e.g., a myeloma cell line) is derived  
5 from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin, and thymidine (HAT medium). Any of a number of myeloma cell lines can be used  
10 as a fusion partner according to standard techniques, e.g., the P3-NS1/1-Ag4-1, P3-x63-Ag8.653, or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC (American Type Culture Collection, Manassas, VA). Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol (PEG). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for  
15 antibodies that bind Gene 216 polypeptides or peptides, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-Gene 216 antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage  
25 display library) with Gene 216 to thereby isolate immunoglobulin library members that bind Gene 216. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP™ Phage Display Kit, Catalog No. 240612).

30 Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in,

for example, Ladner et al. U.S. Pat. No. 5,223,409; Kang et al. PCT International Publication No. WO 92/18619; Dower et al. PCT International Publication No. WO 91/17271; Winter et al. PCT International Publication WO 92/20791; Markland et al. PCT International Publication No. WO 92/15679;

5 Breitling et al. PCT International Publication WO 93/01288; McCafferty et al. PCT International Publication No. WO 92/01047; Garrard et al. PCT International Publication No. WO 92/09690; Ladner et al. PCT International Publication No. WO 90/02809; Fuchs et al., 1991, *Bio/Technology* **9**:1370-1372; Hay et al., 1992, *Hum. Antibod. Hybridomas* **3**:81-85; Huse et al., 1989,

10 *Science* **246**:1275-1281; Griffiths et al., 1993, *EMBO J* **12**:725-734; Hawkins et al., 1992, *J. Mol. Biol.* **226**:889-896; Clarkson et al., 1991, *Nature* **352**:624-628; Gram et al., 1992, *PNAS* **89**:3576-3580; Garrad et al., 1991, *Bio/Technology* **9**:1373-1377; Hoogenboom et al., 1991, *Nuc. Acid Res.* **19**:4133-4137; Barbas et al., 1991, *PNAS* **88**:7978-7982; and McCafferty et al.,

15 1990, *Nature* **348**:552-55.

Additionally, recombinant anti-Gene 216 antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and

20 humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson et al. International Application No. PCT/US86/02269; Akira, et al. European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison et al. European Patent Application 173,494; Neuberger et

25 al. PCT International Publication No. WO 86/01533; Cabilly et al. U.S. Pat. No. 4,816,567; Cabilly et al. European Patent Application 125,023; Better et al., 1988, *Science* **240**:1041-1043; Liu et al., 1987, *PNAS* **84**:3439-3443; Liu et al., 1987, *J. Immunol.* **139**:3521-3526; Sun et al., 1987, *PNAS* **84**:214-218; Nishimura et al., 1987, *Canc. Res.* **47**:999-1005; Wood et al., 1985, *Nature*

30 **314**:446-449; and Shaw et al., 1988, *J. Natl. Cancer Inst.* **80**:1553-1559; S.L. Morrison, 1985, *Science* **229**:1202-1207; Oi et al., 1986, *BioTechniques* **4**:214;

Winter U.S. Pat. No. 5,225,539; Jones et al., 1986, *Nature* **321**:552-525; Verhoeyan et al., 1988, *Science* **239**:1534; and Bcidler et al., 1988, *J. Immunol.* **141**:4053-4060.

5 An anti-Gene 216 antibody (e.g., monoclonal antibody) can be used to isolate Gene 216 by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-Gene 216 antibody can also facilitate the purification of natural Gene 216 polypeptide from cells and of recombinantly produced Gene 216 polypeptides or peptides expressed in host cells. Further, an anti-Gene 216 antibody can be used to detect Gene 216 protein (e.g., in a  
10 cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the Gene 216 protein. Anti-Gene 216 antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen as described in detail herein. In addition, and anti-Gene  
15 216 antibody can be used as therapeutics for the treatment of diseases related to abnormal Gene 216 expression or function, e.g., asthma.

### Ligands

The Gene 216 polypeptides, polynucleotides, variants, or fragments thereof, can be used to screen for ligands (e.g., agonists, antagonists, or  
20 inhibitors) that modulate the levels or activity of the Gene 216 polypeptide. In addition, these Gene 216 molecules can be used to identify endogenous ligands that bind to Gene 216 polypeptides or polynucleotides in the cell. In one aspect of the present invention, the full-length Gene 216 polypeptide (e.g., SEQ ID NO:4) is used to identify ligands. Alternatively, variants or fragments  
25 of a Gene 216 polypeptide are used. Such fragments may comprise, for example, one or more domains of the Gene 216 polypeptide (e.g., the pre-, pro-, catalytic, cysteine-rich, disintegrin, EGF, transmembrane, and cytoplasmic domains) disclosed herein. Of particular interest are screening assays that identify agents that have relatively low levels of toxicity in human cells. A wide  
30 variety of assays may be used for this purpose, including *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays, and the

like.

The term "ligand" as used herein describes any molecule, protein, peptide, or compound with the capability of directly or indirectly altering the physiological function, stability, or levels of the Gene 216 polypeptide. Ligands that bind to the Gene 216 polypeptides or polynucleotides of the invention are potentially useful in diagnostic applications and/or pharmaceutical compositions, as described in detail herein. Ligands may encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 50 and less than about 2,500 daltons. Such ligands can comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. Ligands often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Ligands can also comprise biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof.

Ligands may include, for example, 1) peptides such as soluble peptides, including Ig-tailed fusion peptides and members of random peptide libraries (see, e.g., Lam et al., 1991, *Nature* **354**:82-84; Houghten et al., 1991, *Nature* **354**:84-86) and combinatorial chemistry-derived molecular libraries made of D- and/or L-configuration amino acids; 2) phosphopeptides (e.g., members of random and partially degenerate, directed phosphopeptide libraries, see, e.g., Songyang et al, 1993, *Cell* **72**:767-778); 3) antibodies (e.g., polyclonal, monoclonal, humanized, anti-idiotypic, chimeric, and single chain antibodies as well as Fab, F(ab')<sub>2</sub>, Fab expression library fragments, and epitope-binding fragments of antibodies); and 4) small organic and inorganic molecules.

Ligands can be obtained from a wide variety of sources including libraries of synthetic or natural compounds. Synthetic compound libraries are commercially available from, for example, Maybridge Chemical Co. (Trevillet,

Cornwall, UK), Comgenex (Princeton, NJ), Brandon Associates (Merrimack, NH), and Microsource (New Milford, CT). A rare chemical library is available from Aldrich Chemical Company, Inc. (Milwaukee, WI). Natural compound libraries comprising bacterial, fungal, plant or animal extracts are available  
5 from, for example, Pan Laboratories (Bothell, WA). In addition, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides.

Alternatively, libraries of natural compounds in the form of bacterial,  
10 fungal, plant and animal extracts can be readily produced. Methods for the synthesis of molecular libraries are readily available (see, e.g., DeWitt et al., 1993, *Proc. Natl. Acad. Sci. USA* **90**:6909; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* **91**:11422; Zuckermann et al., 1994, *J. Med. Chem.* **37**:2678; Cho et al., 1993, *Science* **261**:1303; Carell et al., 1994, *Angew. Chem. Int. Ed. Engl.*  
15 **33**:2059; Carell et al., 1994, *Angew. Chem. Int. Ed. Engl.* **33**:2061; and in Gallop et al., 1994, *J. Med. Chem.* **37**:1233). In addition, natural or synthetic compound libraries and compounds can be readily modified through conventional chemical, physical and biochemical means (see, e.g., Blondelle et al., 1996, *Trends in Biotech.* **14**:60), and may be used to produce  
20 combinatorial libraries. In another approach, previously identified pharmacological agents can be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification, and the analogs can be screened for Gene 216-modulating activity.

Numerous methods for producing combinatorial libraries are known in  
25 the art, including those involving biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four  
30 approaches are applicable to polypeptide, non-peptide oligomer, or small molecule libraries of compounds (K. S. Lam, 1997, *Anticancer Drug Des.*

12:145).

Libraries may be screened in solution (e.g., Houghten, 1992, *Biotechniques* **13**:412-421), or on beads (Lam, 1991, *Nature* **354**:82-84), chips (Fodor, 1993, *Nature* **364**:555-556), bacteria or spores (Ladner U.S. Pat. No. 5,223,409), plasmids (Cull et al., 1992, *Proc. Natl. Acad. Sci. USA* **89**:1865-1869), or on phage (Scott and Smith, 1990, *Science* **249**:386-390; Devlin, 1990, *Science* **249**:404-406; Cwirla et al., 1990, *Proc. Natl. Acad. Sci. USA* **97**:6378-6382; Felici, 1991, *J. Mol. Biol.* **222**:301-310; Ladner, *supra*).

Where the screening assay is a binding assay, a Gene 216 polypeptide, polynucleotide, analog, or fragment thereof, may be joined to a label, where the label can directly or indirectly provide a detectable signal. Various labels include radioisotopes, fluorescers, chemiluminescers, enzymes, specific binding molecules, particles, e.g. magnetic particles, and the like. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin, etc. For the specific binding members, the complementary member would normally be labeled with a molecule that provides for detection, in accordance with known procedures.

A variety of other reagents may be included in the screening assay. These include reagents like salts, neutral proteins, e.g. albumin, detergents, etc., that are used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Reagents that improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The components are added in any order that produces the requisite binding. Incubations are performed at any temperature that facilitates optimal activity, typically between 4° and 40°C. Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high-throughput screening. Normally, between 0.1 and 1 hr will be sufficient. In general, a plurality of assay mixtures is run in parallel with different agent concentrations to obtain a differential response to these concentrations. Typically, one of these concentrations serves as a negative control, i.e. at zero concentration or below the level of detection.

To perform cell-free ligand screening assays, it may be desirable to immobilize either the Gene 216 polypeptide, polynucleotide, or fragment to a surface to facilitate identification of ligands that bind to these molecules, as well as to accommodate automation of the assay. For example, a fusion protein comprising a Gene 216 polypeptide and an affinity tag can be produced. In one embodiment, a glutathione-S-transferase/phosphodiesterase fusion protein comprising a Gene 216 polypeptide is adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione-derivatized microtiter plates. Cell lysates (e.g., containing <sup>35</sup>S-labeled polypeptides) are added to the Gene 216-coated beads under conditions to allow complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the Gene 216-coated beads are washed to remove any unbound polypeptides, and the amount of immobilized radiolabel is determined. Alternatively, the complex is dissociated and the radiolabel present in the supernatant is determined. In another approach, the beads are analyzed by SDS-PAGE to identify Gene 216-binding polypeptides.

Ligand-binding assays can be used to identify agonist or antagonists that alter the function or levels of the Gene 216 polypeptide. Such assays are designed to detect the interaction of test agents with Gene 216 polypeptides, polynucleotides, analogs, or fragments thereof. Interactions may be detected by direct measurement of binding. Alternatively, interactions may be detected by indirect indicators of binding, such as stabilization/destabilization of protein structure, or activation/inhibition of biological function. Non-limiting examples of useful ligand-binding assays are detailed below.

Ligands that bind to Gene 216 polypeptides, polynucleotides, analogs, or fragments thereof, can be identified using real-time Bimolecular Interaction Analysis (BIA; Sjolander et al., 1991, *Anal. Chem.* **63**:2338-2345; Szabo et al., 1995, *Curr. Opin. Struct. Biol.* **5**:699-705). BIA-based technology (e.g., BIAcore<sup>TM</sup>; LKB Pharmacia, Sweden) allows study of biospecific interactions in real time, without labeling. In BIA, changes in the optical phenomenon surface plasmon resonance (SPR) is used determine real-time interactions of



biological molecules.

Ligands can also be identified by scintillation proximity assays (SPA, described in U.S. Patent No. 4,568,649). In a modification of this assay that is currently undergoing development, chaperonins are used to distinguish  
5 folded and unfolded proteins. A tagged protein is attached to SPA beads, and test agents are added. The bead is then subjected to mild denaturing conditions (such as, e.g., heat, exposure to SDS, etc.) and a purified labeled chaperonin is added. If a test agent binds to a target, the labeled chaperonin will not bind; conversely, if no test agent binds, the protein will undergo some  
10 degree of denaturation and the chaperonin will bind.

Ligands can also be identified using a binding assay based on mitochondrial targeting signals (Hurt et al., 1985, *EMBO J.* **4**:2061-2068; Eilers and Schatz, 1986, *Nature* **322**:228-231). In a mitochondrial import assay, expression vectors are constructed in which nucleic acids encoding particular  
15 target proteins are inserted downstream of sequences encoding mitochondrial import signals. The chimeric proteins are synthesized and tested for their ability to be imported into isolated mitochondria in the absence and presence of test compounds. A test compound that binds to the target protein should inhibit its uptake into isolated mitochondria *in vitro*.

20 The ligand-binding assay described in Fodor et al., 1991, *Science* **251**:767-773, which involves testing the binding affinity of test compounds for a plurality of defined polymers synthesized on a solid substrate, can also be used.

Ligands that bind to Gene 216 polypeptides or peptides can be  
25 identified using two-hybrid assays (see, e.g., U.S. Pat. No. 5,283,317; Zervos et al., 1993, *Cell* **72**:223-232; Madura et al., 1993, *J. Biol. Chem.* **268**:12046-12054; Bartel et al., 1993, *Biotechniques* **14**:920-924; Iwabuchi et al., 1993, *Oncogene* **8**:1693-1696; and Brent WO 94/10300). The two-hybrid system relies on the reconstitution of transcription activation activity by association of  
30 the DNA-binding and transcription activation domains of a transcriptional activator through protein-protein interaction. The yeast GAL4 transcriptional

activator may be used in this way, although other transcription factors have been used and are well known in the art. To carry out the two-hybrid assay, the GAL4 DNA-binding domain, and the GAL4 transcription activation domain are expressed, separately, as fusions to potential interacting polypeptides.

5           In one embodiment, the "bait" protein comprises a Gene 216 polypeptide fused to the GAL4 DNA-binding domain. The "fish" protein comprises, for example, a human cDNA library encoded polypeptide fused to the GAL4 transcription activation domain. If the two, coexpressed fusion proteins interact in the nucleus of a host cell, a reporter gene (e.g. LacZ) is  
10           activated to produce a detectable phenotype. The host cells that show two-hybrid interactions can be used to isolate the containing plasmids containing the cDNA library sequences. These plasmids can be analyzed to determine the nucleic acid sequence and predicted polypeptide sequence of the candidate ligand. Alternatively, methods such as the three-hybrid (Licitra et al.,  
15           1996, *Proc. Natl. Acad. Sci. USA* **93**:12817-12821), and reverse two-hybrid (Vidal et al., 1996, *Proc. Natl. Acad. Sci. USA* **93**:10315-10320) systems may be used. Commercially available two-hybrid systems such as the CLONTECH Matchmaker™ systems and protocols (CLONTECH Laboratories, Inc., Palo Alto, CA) may be also be used (see also, A.R. Mendelsohn et al., 1994, *Curr.*  
20           *Op. Biotech.* **5**:482; E.M. Phizicky et al., 1995, *Microbiological Rev.* **59**:94; M. Yang et al., 1995, *Nucleic Acids Res.* **23**:1152; S. Fields et al., 1994, *Trends Genet.* **10**:286; and U.S. Patent No. 6,283,173 and 5,468,614).

          Several methods of automated assays have been developed in recent years so as to permit screening of tens of thousands of test agents in a short  
25           period of time. High-throughput screening methods are particularly preferred for use with the present invention. The ligand-binding assays described herein can be adapted for high-throughput screens, or alternative screens may be employed. For example, continuous format high throughput screens (CF-HTS) using at least one porous matrix allows the researcher to test large numbers  
30           of test agents for a wide range of biological or biochemical activity (see United States Patent No. 5,976,813 to Beutel et al.). Moreover, CF-HTS can be used

to perform multi-step assays.

### **Diagnostics**

As discussed herein, chromosomal region 20p13-p12 has been genetically linked to a variety of diseases and disorders, including asthma. The present invention provides nucleic acids and antibodies that can be useful in diagnosing individuals with aberrant Gene 216 expression. In particular, the disclosed SNPs, alleles, and haplotypes can be used to diagnose chromosomal abnormalities linked to these diseases.

Antibody-based diagnostic methods: In a further embodiment of the present invention, antibodies which specifically bind to the Gene 216 polypeptide may be used for the diagnosis of conditions or diseases characterized by underexpression or overexpression of the Gene 216 polynucleotide or polypeptide, or in assays to monitor patients being treated with a Gene 216 polypeptide or peptide, or a Gene 216 agonist, antagonist, or inhibitor.

The antibodies useful for diagnostic purposes may be prepared in the same manner as those for use in therapeutic methods, described herein. Antibodies may be raised to the full-length Gene 216 polypeptide sequence (e.g., SEQ ID NO:4). Alternatively, the antibodies may be raised to fragments or variants of the Gene 216 polypeptide. In one aspect of the invention, antibodies are prepared to bind to a Gene 216 polypeptide fragment comprising one or more domains of the Gene 216 polypeptide (e.g., pre-, pro-, catalytic, disintegrin, cysteine-rich, EGF, transmembrane, and cytoplasmic domains) described herein.

Diagnostic assays for the Gene 216 polypeptide include methods that utilize the antibody and a label to detect the protein in biological samples (e.g., human body fluids, cells, tissues, or extracts of cells or tissues). The antibodies may be used with or without modification, and may be labeled by joining them, either covalently or non-covalently, with a reporter molecule. A wide variety of reporter molecules that are known in the art may be used, several of which are described herein.

The invention provides methods for detecting disease-associated antigenic components in a biological sample, which methods comprise the steps of: 1) contacting a sample suspected to contain a disease-associated antigenic component with an antibody specific for an disease-associated antigen, extracellular or intracellular, under conditions in which an antigen-antibody complex can form between the antibody and disease-associated antigenic components in the sample; and 2) detecting any antigen-antibody complex formed in step (1) using any suitable means known in the art, wherein the detection of a complex indicates the presence of disease-associated antigenic components in the sample. It will be understood that assays that utilize antibodies directed against altered Gene 216 amino acid sequences (i.e., epitopes encoded by SNP-related alleles or haplotypes, or mutations, or other variants) are within the scope of the invention.

Many immunoassay formats are known in the art, and the particular format used is determined by the desired application. An immunoassay can use, for example, a monoclonal antibody directed against a single disease-associated epitope, a combination of monoclonal antibodies directed against different epitopes of a single disease-associated antigenic component, monoclonal antibodies directed towards epitopes of different disease-associated antigens, polyclonal antibodies directed towards the same disease-associated antigen, or polyclonal antibodies directed towards different disease-associated antigens. Protocols can also, for example, use solid supports, or may involve immunoprecipitation.

In accordance with the present invention, "competitive" (U.S. Pat. Nos. 3,654,090 and 3,850,752), "sandwich" (U.S. Pat. No. 4,016,043), and "double antibody," or "DASP" assays may be used. Several procedures for measuring the Gene 216 polypeptide (e.g., ELISA, RIA, and FACS) are known in the art and provide a basis for diagnosing altered or abnormal levels of Gene 216 polypeptide expression. Normal or standard values for Gene 216 polypeptide expression are established by incubating biological samples taken from normal subjects, preferably human, with antibody to the Gene polypeptide under

conditions suitable for complex formation. The amount of standard complex formation may be quantified by various methods; photometric means are preferred. Levels of the Gene 216 polypeptide expressed in the subject sample, negative control (normal) sample, and positive control (disease) sample are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

Typically, immunoassays use either a labeled antibody or a labeled antigenic component (e.g., that competes with the antigen in the sample for binding to the antibody). A number of fluorescent materials are known and can be utilized as labels for antibodies or polypeptides. These include, for example, Cy3, Cy5, Alexa, BODIPY, fluorescein (e.g., FluorX, DTAF, and FITC), rhodamine (e.g., TRITC), auramine, Texas Red, AMCA blue, and Lucifer Yellow. Antibodies or polypeptides can also be labeled with a radioactive element or with an enzyme. Preferred isotopes include  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{36}\text{Cl}$ ,  $^{51}\text{Cr}$ ,  $^{57}\text{Co}$ ,  $^{58}\text{Co}$ ,  $^{59}\text{Fe}$ ,  $^{90}\text{Y}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ , and  $^{186}\text{Re}$ . Preferred enzymes include peroxidase,  $\beta$ -glucuronidase,  $\beta$ -D-glucosidase,  $\beta$ -D-galactosidase, urease, glucose oxidase plus peroxidase, and alkaline phosphatase (see, e.g., U.S. Pat. Nos. 3,654,090; 3,850,752 and 4,016,043). Enzymes can be conjugated by reaction with bridging molecules such as carbodiimides, diisocyanates, glutaraldehyde, and the like. Enzyme labels can be detected visually, or measured by calorimetric, spectrophotometric, fluorospectrophotometric, amperometric, or gasometric techniques. Other labeling systems, such as avidin/biotin, Tyramide Signal Amplification (TSA<sup>TM</sup>), are known in the art, and are commercially available (see, e.g., ABC kit, Vector Laboratories, Inc., Burlingame, CA; NEN<sup>®</sup> Life Science Products, Inc., Boston, MA).

Kits suitable for antibody-based diagnostic applications typically include one or more of the following components:

(1) Antibodies: The antibodies may be pre-labeled; alternatively, the antibody may be unlabeled and the ingredients for labeling may be included in the kit in separate containers, or a secondary, labeled antibody is provided;

and

(2) Reaction components: The kit may also contain other suitably packaged reagents and materials needed for the particular immunoassay protocol, including solid-phase matrices, if applicable, and standards.

5       The kits referred to above may include instructions for conducting the test. Furthermore, in preferred embodiments, the diagnostic kits are adaptable to high-throughput and/or automated operation.

Nucleic-acid-based diagnostic methods: The invention provides methods for altered levels or sequences of Gene 216 nucleic acids in a sample, such as in a biological sample, which methods comprise the steps of:

10       1) contacting a sample suspected to contain a disease-associated nucleic acid with one or more disease-associated nucleic acid probes under conditions in which hybrids can form between any of the probes and disease-associated nucleic acid in the sample; and 2) detecting any hybrids formed in step (1)

15       using any suitable means known in the art, wherein the detection of hybrids indicates the presence of the disease-associated nucleic acid in the sample.

      To detect disease-associated nucleic acids present in low levels in biological samples, it may be necessary to amplify the disease-associated sequences or the hybridization signal as part of the diagnostic assay. Techniques for

20       amplification are known to those of skill in the art.

      The presence of Gene 216 polynucleotide sequences can be detected by DNA-DNA or DNA-RNA hybridization, or by amplification using probes or primers comprising at least a portion of a Gene 216 polynucleotide, or a sequence complementary thereto. In particular, nucleic acid amplification-

25       based assays can use Gene 216 oligonucleotides or oligomers to detect transformants containing Gene 216 DNA or RNA. Gene 216 nucleic acids useful as probes in diagnostic methods include oligonucleotides at least 15 nucleotides in length, preferably at least 20 nucleotides in length, and most preferably at least 25-55 nucleotides in length, that hybridize specifically with

30       Gene 216 nucleic acids.

      Several methods can be used to produce specific probes for Gene 216

polynucleotides. For example, labeled probes can be produced by oligo-labeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, Gene 216 polynucleotide sequences (e.g., SEQ ID NO:1 or SEQ ID NO:6), or any portions or fragments thereof, may be cloned  
5 into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by addition of an appropriate RNA polymerase, such as T7, T3, or SP(6) and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits (e.g., from Amersham-Pharmacia;  
10 Promega Corp.; and U.S. Biochemical Corp., Cleveland, OH). Suitable reporter molecules or labels which may be used include radionucleotides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

A sample to be analyzed, such as, for example, a tissue sample (e.g.,  
15 hair or buccal cavity) or body fluid sample (e.g., blood or saliva), may be contacted directly with the nucleic acid probes. Alternatively, the sample may be treated to extract the nucleic acids contained therein. It will be understood that the particular method used to extract DNA will depend on the nature of the biological sample. The resulting nucleic acid from the sample may be  
20 subjected to gel electrophoresis or other size separation techniques, or, the nucleic acid sample may be immobilized on an appropriate solid matrix without size separation.

Kits suitable for nucleic acid-based diagnostic applications typically include the following components:

25 (1) Probe DNA: The probe DNA may be prelabeled; alternatively, the probe DNA may be unlabeled and the ingredients for labeling may be included in the kit in separate containers; and

(2) Hybridization reagents: The kit may also contain other suitably packaged reagents and materials needed for the particular hybridization  
30 protocol, including solid-phase matrices, if applicable, and standards.

In cases where a disease condition is suspected to involve an alteration

of the Gene 216 nucleotide sequence, specific oligonucleotides may be constructed and used to assess the level of disease mRNA in cells affected or other tissue affected by the disease. For example, PCR can be used to test whether a person has a disease-related polymorphism (i.e., mutation).

5 For PCR analysis, Gene 216 oligonucleotides may be chemically synthesized, generated enzymatically, or produced from a recombinant source. Oligomers will preferably comprise two nucleotide sequences, one with a sense orientation (5' → 3') and another with an antisense orientation (3' → 5'), employed under optimized conditions for identification of a specific gene or  
10 condition. The same two oligomers, nested sets of oligomers, or even a degenerate pool of oligomers may be employed under less stringent conditions for detection and/or quantification of closely related DNA or RNA sequences.

In accordance with PCR analysis, two oligonucleotides are synthesized by standard methods or are obtained from a commercial supplier of custom-made oligonucleotides. The length and base composition are determined by  
15 standard criteria using the Oligo 4.0 primer Picking program (W. Rychlik, 1992; available from Molecular Biology Insights, Inc., Cascade, CO). One of the oligonucleotides is designed so that it will hybridize only to the disease gene DNA under the PCR conditions used. The other oligonucleotide is designed  
20 to hybridize a segment of genomic DNA such that amplification of DNA using these oligonucleotide primers produces a conveniently identified DNA fragment. Samples may be obtained from hair follicles, whole blood, or the buccal cavity. The DNA fragment generated by this procedure is sequenced by standard techniques.

25 In one particular aspect, Gene 216 oligonucleotides can be used to perform Genetic Bit Analysis (GBA) of Gene 216 in accordance with published methods (T.T. Nikiforov et al., 1994, *Nucleic Acids Res.* **22**(20):4167-75; T.T. Nikiforov et al., 1994, *PCR Methods Appl.* **3**(5):285-91). In PCR-based GBA, specific fragments of genomic DNA containing the polymorphic site(s)  
30 are first amplified by PCR using one unmodified and one phosphorothioate-modified primer. The double-stranded PCR product is rendered single-



stranded and then hybridized to immobilized oligonucleotide primer in wells of a multi-well plate. The primer is designed to anneal immediately adjacent to the polymorphic site of interest. The 3' end of the primer is extended using a mixture of individually labeled dideoxynucleoside triphosphates. The label on  
5 the extended base is then determined. Preferably, GBA is performed using semi-automated ELISA or biochip formats (see, e.g., S.R. Head et al., 1997, *Nucleic Acids Res.* **25**(24):5065-71; T.T. Nikiforov et al., 1994, *Nucleic Acids Res.* **22**(20):4167-75).

Other amplification techniques besides PCR may be used as  
10 alternatives, such as ligation-mediated PCR or techniques involving Q-beta replicase (Cahill et al., 1991, *Clin. Chem.*, **37**(9):1482-5). Products of amplification can be detected by agarose gel electrophoresis, quantitative hybridization, or equivalent techniques for nucleic acid detection known to one skilled in the art of molecular biology (Sambrook et al., 1989). Other alterations  
15 in the disease gene may be diagnosed by the same type of amplification-detection procedures, by using oligonucleotides designed to contain and specifically identify those alterations.

Gene 216 polynucleotides may also be used to detect and quantify levels of Gene 216 mRNA in biological samples in which altered expression of  
20 Gene 216 polynucleotide may be correlated with disease. These diagnostic assays may be used to distinguish between the absence, presence, increase, and decrease of Gene 216 mRNA levels, and to monitor regulation of Gene 216 polynucleotide levels during therapeutic treatment or intervention. For example, Gene 216 polynucleotide sequences, or fragments, or  
25 complementary sequences thereof, can be used in Southern or Northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; or in dip stick, pin, ELISA or biochip assays utilizing fluids or tissues from patient biopsies to detect the status of, e.g., levels or overexpression of Gene 216, or to detect altered Gene 216 expression. Such  
30 qualitative or quantitative methods are well known in the art (G.H. Keller and M.M. Manak, 1993, *DNA Probes*, 2<sup>nd</sup> Ed, Macmillan Publishers Ltd., England;

D.W. Dieffenbach and G. S. Dveksler, 1995, *PCR Primer: A Laboratory Manual*, Cold Spring Harbor Press, Plainview, NY; B.D. Hames and S.J. Higgins, 1985, *Gene Probes 1, 2*, IRL Press at Oxford University Press, Oxford, England).

5           Methods suitable for quantifying the expression of Gene 216 include radiolabeling or biotinylating nucleotides, co-amplification of a control nucleic acid, and standard curves onto which the experimental results are interpolated (P.C. Melby et al., 1993, *J. Immunol. Methods* **159**:235-244; and C. Duplaa et al., 1993, *Anal. Biochem.* 229-236). The speed of quantifying multiple samples  
10       may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantification.

          In accordance with these methods, the specificity of the probe, i.e., whether it is made from a highly specific region (e.g., at least 8 to 10 or 12 or  
15       15 contiguous nucleotides in the 5' regulatory region), or a less specific region (e.g., especially in the 3' coding region), and the stringency of the hybridization or amplification (e.g., high, intermediate, or low) will determine whether the probe identifies only naturally occurring sequences encoding the Gene 216 polypeptide, alleles thereof, or related sequences.

20       In a particular aspect, a Gene 216 nucleic acid sequence, or a sequence complementary thereto, or fragment thereof, may be useful in assays that detect Gene 216-related diseases such as asthma. The Gene 216 polynucleotide can be labeled by standard methods, and added to a biological sample from a subject under conditions suitable for the formation of  
25       hybridization complexes. After a suitable incubation period, the sample can be washed and the signal is quantified and compared with a standard value. If the amount of signal in the test sample is significantly altered from that of a comparable negative control (normal) sample, the altered levels of Gene 216 nucleotide sequence can be correlated with the presence of the associated  
30       disease. Such assays may also be used to evaluate the efficacy of a particular prophylactic or therapeutic regimen in animal studies, in clinical trials, or for an

individual patient.

To provide a basis for the diagnosis of a disease associated with altered expression of Gene 216, a normal or standard profile for expression is established. This may be accomplished by incubating biological samples taken  
5 from normal subjects, either animal or human, with a sequence complementary to the Gene 216 polynucleotide, or a fragment thereof, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with those from an experiment where a known amount of a substantially purified  
10 polynucleotide is used. Standard values obtained from normal samples may be compared with values obtained from samples from patients who are symptomatic for the disease. Deviation between standard and subject (patient) values is used to establish the presence of the condition.

Once the disease is diagnosed and a treatment protocol is initiated,  
15 hybridization assays may be repeated on a regular basis to evaluate whether the level of expression in the patient begins to approximate that which is observed in a normal individual. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

20 With respect to diseases such as asthma, the presence of an abnormal amount of Gene 216 transcript in a biological sample (e.g., body fluid, cells, tissues, or cell or tissue extracts) from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A  
25 more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier, thereby preventing the development or further progression of the disease.

Microarrays: In another embodiment of the present invention, oligonucleotides, or longer fragments derived from the Gene 216  
30 polynucleotide sequence described herein may be used as targets in a microarray (e.g., biochip) system. The microarray can be used to monitor the

expression level of large numbers of genes simultaneously (to produce a transcript image), and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disease, to diagnose disease, and to develop and monitor the activities of therapeutic or prophylactic agents. Preparation and use of microarrays have been described in WO 95/11995 to Chee et al.; D.J. Lockhart et al., 1996, *Nature Biotechnology* **14**:1675-1680; M. Schena et al., 1996, *Proc. Natl. Acad. Sci. USA* **93**:10614-10619; U.S. Patent No. 6,015,702 to P. Lal et al.; J. Worley et al., 2000, *Microarray Biochip Technology*, M. Schena, ed., Biotechniques Book, Natick, MA, pp. 65-86; Y.H. Rogers et al., 1999, *Anal. Biochem.* **266**(1):23-30; S.R. Head et al., 1999, *Mol. Cell. Probes.* **13**(2):81-7; S.J. Watson et al., 2000, *Biol. Psychiatry* **48**(12):1147-56.

In one application of the present invention, microarrays containing arrays of Gene 216 polynucleotide sequences can be used to measure the expression levels of Gene 216 in an individual. In particular, to diagnose an individual with a Gene 216-related condition or disease, a sample from a human or animal (containing nucleic acids, e.g., mRNA) can be used as a probe on a biochip containing an array of Gene 216 polynucleotides (e.g., DNA) in decreasing concentrations (e.g., 1 ng, 0.1 ng, 0.01 ng, etc.). The test sample can be compared to samples from diseased and normal samples. Biochips can also be used to identify Gene 216 mutations or polymorphisms in a population, including but not limited to, deletions, insertions, and mismatches. For example, mutations can be identified by: 1) placing Gene 216 polynucleotides of this invention onto a biochip; 2) taking a test sample (containing, e.g., mRNA) and adding the sample to the biochip; 3) determining if the test samples hybridize to the Gene 216 polynucleotides attached to the chip under various hybridization conditions (see, e.g., V.R. Chechetkin et al., 2000, *J. Biomol. Struct. Dyn.* **18**(1):83-101). Alternatively microarray sequencing can be performed (see, e.g., E.P. Diamandis, 2000, *Clin. Chem.* **46**(10):1523-5).

Chromosome mapping: In another application of this invention, the Gene 216 nucleic acid sequence, or a complementary sequence, or fragment thereof, can be used as probes which are useful for mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to human artificial chromosome constructions (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial PI constructions, or single chromosome cDNA libraries (see C.M. Price, 1993, *Blood Rev.*, 7:127-134 and by B.J. Trask, 1991, *Trends Genet.* 7:149-154).

In another of its aspects, the invention relates to a diagnostic kit for detecting Gene 216 polynucleotide or polypeptide as it relates to a disease or susceptibility to a disease, particularly asthma. Also related is a diagnostic kit that can be used to detect or assess asthma conditions. Such kits comprise one or more of the following:

(a) a Gene 216 polynucleotide, preferably the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:6, or a fragment thereof; or

(b) a nucleotide sequence complementary to that of (a); or

(c) a Gene 216 polypeptide, preferably the polypeptide of SEQ ID NO:4, or a fragment thereof; or

(d) an antibody to a Gene 216 polypeptide, preferably to the polypeptide of SEQ ID NO:4, or an antibody bindable fragment thereof. It will be appreciated that in any such kits, (a), (b), (c), or (d) may comprise a substantial component and that instructions for use can be included. The kits may also contain peripheral reagents such as buffers, stabilizers, etc.

The present invention also includes a test kit for genetic screening that can be utilized to identify mutations in Gene 216. By identifying patients with mutated Gene 216 DNA and comparing the mutation to a database that contains known mutations in Gene 216 and a particular condition or disease, identification and/or confirmation of, a particular condition or disease can be made. Accordingly, such a kit would comprise a PCR-based test that would involve transcribing the patients mRNA with a specific primer, and amplifying

the resulting cDNA using another set of primers. The amplified product would be detectable by gel electrophoresis and could be compared with known standards for Gene 216. Preferably, this kit would utilize a patient's blood, serum, or saliva sample, and the DNA would be extracted using standard techniques. Primers flanking a known mutation would then be used to amplify a fragment of Gene 216. The amplified piece would then be sequenced to determine the presence of a mutation.

Genomic Screening: The use of polymorphic genetic markers linked to the Gene 216 gene is very useful in predicting susceptibility to the diseases genetically linked to 20p13-p12. Similarly, the identification of polymorphic genetic markers within the Gene 216 gene will allow the identification of specific allelic variants that are in linkage disequilibrium with other genetic lesions that affect one of the disease states discussed herein including respiratory disorders, obesity, and inflammatory bowel disease. SSCP (see below) allows the identification of polymorphisms within the genomic and coding region of the disclosed gene. The present invention provides sequences for primers that can be used identify exons that contain SNPs and the corresponding alleles, as well as sequences for primers that can be used to identify the sequence change. This information can be used to identify additional SNPs, alleles, and haplotypes in accordance with the methods disclosed herein. Suitable methods for genomic screening have also been described by, e.g., Sheffield et al., 1995, *Genet.*, 4:1837-1844; LeBlanc-Straceski et al., 1994, *Genomics*, 19:341-9; Chen et al., 1995, *Genomics*, 25:1-8. In employing these methods, the disclosed reagents can be used to predict the risk for disease (e.g., respiratory disorders, obesity, and inflammatory bowel disease) in a population or individual.

### Therapeutics

The present invention provides methods of screening for drugs comprising contacting such an agent with a novel protein of this invention or fragment thereof and assaying 1) for the presence of a complex between the agent and the protein or fragment, or 2) for the presence of a complex between

the protein or fragment and a ligand, by methods well known in the art. In such competitive binding assays the novel protein or fragment is typically labeled. Free protein or fragment is separated from that present in a protein:protein complex, and the amount of free (i.e., uncomplexed) label is a measure of the binding of the agent being tested to Gene 216 protein or its interference with protein ligand binding, respectively.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of specifically binding the Gene 216 protein compete with a test compound for binding to the Gene 216 protein or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants of a Gene 216 protein.

The goal of rational drug design is to produce structural analogs of biologically active proteins of interest or of small molecules with which they interact (e.g., agonists, antagonists, inhibitors) in order to fashion drugs which are, for example, more active or stable forms of the protein, or which, e.g., enhance or interfere with the function of a protein *in vivo* (see, e.g., Hodgson, 1991, *Bio/Technology*, 9:19-21). In one approach, one first determines the three-dimensional structure of a protein of interest or, for example, of the Gene 216 receptor or ligand complex, by x-ray crystallography, by computer modeling or most typically, by a combination of approaches. Less often, useful information regarding the structure of a protein may be gained by modeling based on the structure of homologous proteins. An example of rational drug design is the development of HIV protease inhibitors (Erickson et al., 1990, *Science*, 249:527-533). In addition, peptides (e.g., Gene 216 protein) are analyzed by an alanine scan (Wells, 1991, *Methods in Enzymol.*, 202:390-411). In this technique, an amino acid residue is replaced by Ala, and its effect on the peptide's activity is determined. Each of the amino acid residues of the peptide is analyzed in this manner to determine the important regions of the peptide.

It is also possible to isolate a target-specific antibody, selected by a

functional assay, and then to solve its crystal structure. In principle, this approach yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active  
5 antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original Gene 216 protein. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced banks of peptides. Selected peptides would then act as the pharmacore.

10 Thus, one may design drugs which result in, for example, altered Gene 216 protein activity or stability or which act as inhibitors, agonists, antagonists, etc. of Gene 216 protein activity. By virtue of the availability of cloned Gene 216 gene sequences, sufficient amounts of the Gene 216 protein may be made available to perform such analytical studies as x-ray crystallography. In  
15 addition, the knowledge of the Gene 216 polypeptide sequence will guide those employing computer-modeling techniques in place of, or in addition to x-ray crystallography.

In another aspect of the present invention, cells and animals that carry the Gene 216 gene or an analog thereof can be used as model systems to  
20 study and test for substances that have potential as therapeutic agents. After a test substance is administered to animals or applied to the cells, the phenotype of the animals/cells can be determined.

In yet another aspect of this invention, antibodies that specifically react with Gene 216 polypeptide or peptides derived therefrom can be used as  
25 therapeutics. In particular, anti-Gene 216 antibodies can be used to block the Gene 216 activity. Anti-Gene 216 antibodies or fragments thereof can be formulated as pharmaceutical compositions and administered to a subject. It is noted that antibody-based therapeutics produced from non-human sources can cause an undesired immune response in human subjects. To minimize  
30 this problem, chimeric antibody derivatives can be produced. Chimeric antibodies combine a non-human animal variable region with a human



constant region. Chimeric antibodies can be constructed according to methods known in the art (see Morrison et al., 1985, *Proc. Natl. Acad. Sci. USA* **81**:6851; Takeda et al., 1985, *Nature* **314**:452; U.S. Patent No. 4,816,567 of Cabilly et al.; U.S. Patent No. 4,816,397 of Boss et al.; European Patent  
5 Publication EP 171496; EP 0173494; United Kingdom Patent GB 2177096B).

In addition, antibodies can be further "humanized" by any of the techniques known in the art, (e.g., Teng et al., 1983, *Proc. Natl. Acad. Sci. USA* **80**:7308-7312; Kozbor et al., 1983, *Immunology Today* **4**: 7279; Olsson et al., 1982, *Meth. Enzymol.* **92**:3-16; International Patent Application WO92/06193; EP  
10 0239400). Humanized antibodies can also be obtained from commercial sources (e.g., Scotgen Limited, Middlesex, Great Britain). Immunotherapy with a humanized antibody may result in increased long-term effectiveness for the treatment of chronic disease situations or situations requiring repeated antibody treatments.

In one embodiment, compositions (e.g., pharmaceutical compositions) for use with the present invention comprise metalloprotease inhibitors, or analogs or derivatives thereof. Non-limiting examples of metalloprotease inhibitors include: 1) naturally occurring inhibitors, e.g., oprin (J.J. Catanese and L.F. Kress, 1992, *Biochemistry* **31**:410-418; HSF (Y. Yamakawa and T.  
20 Omori-Satoh, 1992, *J. Biochem.* **112**:583-589); erinacin (D. Mebs et al., 1996, *Toxicon* **34**:1313-1316; Omori-Satoh et al., 2000, *Toxicon* **38**:1561-1580); DM40 and DM43 (A.G. Neves-Ferreira et al., 2000, *Biochem. Biophys. Acta.* **1473**:309-320); citrate (B. Francis et al., 1992, *Toxicon* **30**:1239-1246); TIMP-1 and TIMP-2 (R.V. Ward et al., 1991, *Biochem J.* **278**, Pt 1:179-873);  
25 pyrophosphate (G.S. Makowski and M.L. Ramsby, 1999, *Inflammation* **23**:333-360); proglutamyl peptides such as pyroGlu-Asn-Trp-OH and pyroGlu-Glu-Trp-OH (A. Robeva et al., 1991, *Biomed. Biochem. Acta.* **50**:769-773); 2) peptide analogs and derivatives, e.g., 2-distereomeric furan-2-carbonylamino-3-oxohexahydroindolizino[8,7-b]indole carboxylates (S. D'Alessio et al., 2001, *Eur. J. Med. Chem.* **36**:43-53); phosphonate and carboxylate derivatives of  
30 pyroGlu-Asn-Trp-OH (D'Alessio et al., 2001); POL 647 and POL 656 (F.X.

Gomis-Ruth et al., 1998, *Prot. Sci.* **7**:283-292); cysteine-switches (K. Nomura and N. Suzuki, 1993, *FEBS Lett.* **321**:84-88); 3) hydroxamate compounds, e.g., batimastat/BB-94 (see, e.g., G.F. Beattie et al., 1998, *Clin. Cancer Res.* **8**:1899-1902); prinomastat/AG3340 (see, e.g., R. Scatena, 2000, *Expert Opin. Investig. Drugs* **9**:2159-2165); and 4) other inhibitors, e.g., ortho-substituted macrocyclic lactams (G.M. Ksander, 1997, *J. Med. Chem.* **40**:495-505); diketopiperazine (DKP) (A.K. Szardenings et al., 1998, *J. Med. Chem.* **41**(13):2194-200; alendronate/PCP (Makowski and Ramsby, 1999); and CT1746 (Z. An et al., 1997, *Clin. Exp. Metastasis* **15**:184-195).

In particular, the determined structures of metalloproteases and metalloprotease inhibitors can be used to devise Gene 216-targeted inhibitors (i.e., by rational drug design; see Szardenings et al, 1998). Structural information can be found in, e.g., C. Oefner et al., 2000, *J. Mol. Biol.* **296**(2):341-9; B. Wu et al., 2000, *J. Mol. Biol.* **295**(2):257-68; L. Chen et al., 1999, *J. Mol. Biol.* **293**(3):545-57; C. Fernandez-Catalan et al., 1998, *EMBO J.* **17**(17):5238-48; S. Arumugam et al., 1998, *Biochemistry* **37**(27):9650-7; Gohlke et al., 1996, *FEBS Lett.* **378**:126-130; Gomis-Ruth et al., 1998; F.X. Gomis-Ruth et al, 1993, *EMBO J.* **12**:4151-4157; F.X. Gomis-Ruth et al, 1996, *J. Mol. Biol.* **264**:556-566; K. Maskos et al., 1998, *Proc. Natl. Acad. Sci. USA* **95**(7):3408-12; F.X. Gomis-Ruth et al, 1997, *Nature* **389**:77-80; M. Betz et al., 1997, *Eur. J. Biochem.* **247**(1):356-63; B. Lovejoy et al., 1994, *Biochemistry* **33**(27):8207-17. Structures of zinc metalloproteases are also found in Molecular Modeling DataBase (MMDB) at the NCBI website (hypertext transfer protocol on the world wide web at [ncbi.nlm.nih.gov:80/Structure/MMDB/mmdb.shtml](http://ncbi.nlm.nih.gov:80/Structure/MMDB/mmdb.shtml); e.g. Accession Nos. 1D5J, 1D8F, 1D7X, 1BSK, 2TLX, 1TLX, 1BUD, 1BSW, 1UEA, 4AIG, 3AIG, 2AIG, 1KUH, 1DTH, 1UMS, 1UMT, 7TLN, 6TMN, 5TMN, 5TLN, 4TMN, 4TLN, 3TMN, 2TMN, 1TMN, 1TLP, 1IAG, 1HYT, 1AST, 8TLN, 1THL). In an alternative approach, the binding specificity of TIMP proteins can be engineered to produce inhibitors that specifically inactivate Gene 216 polypeptide (see, e.g., H. Nagase et al., 1999, *Ann. NY Acad. Sci.* **878**:1-11; G.S. Butler et al., 1999, *J. Biol. Chem.* **274**(29):20391-

20396).

In another embodiment of the present invention, compositions (e.g., pharmaceutical compositions) for use with the present invention comprise disintegrin agonists, or analogs or derivatives thereof. The determined  
5 structures of disintegrin proteins and domains can be used to devise Gene 216 disintegrin-targeted agonists (i.e., by rational drug design). Such structural information can be found in R.A. Atkinson et al., 1994, *Int. J. Pept. Protein Res.* **43**:563-72; V. Saudek et al., 1991, *Eur. J. Biochem.* **202**:329-38; H. Minoux et al., 2000, *J. Comput. Aided Mol. Des.* **14**:317-27.

10 The present invention contemplates compositions comprising a Gene 216 polynucleotide, polypeptide, antibody, ligand (e.g., agonist, antagonist, or inhibitor), or fragments, variants, or analogs thereof, and a physiologically acceptable carrier, excipient, or diluent as described in detail herein. The present invention further contemplates pharmaceutical compositions useful in  
15 practicing the therapeutic methods of this invention. Preferably, a pharmaceutical composition includes, in admixture, a pharmaceutically acceptable excipient (carrier) and one or more of a Gene 216 polypeptide, polynucleotide, ligand, antibody, or fragment or variant thereof, as described herein, as an active ingredient. The preparation of pharmaceutical  
20 compositions that contain Gene 216-related reagents as active ingredients is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions, however, solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified. The active therapeutic  
25 ingredient is often mixed with excipients that are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH-buffering agents, which  
30 enhance the effectiveness of the active ingredient.

A Gene 216 polypeptide, polynucleotide, ligand, antibody, or variant or

fragment thereof can be formulated into the pharmaceutical composition as neutralized physiologically acceptable salt forms. Suitable salts include the acid addition salts (i.e., formed with the free amino groups of the polypeptide or antibody molecule) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed from the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

The pharmaceutical compositions can be administered systemically by oral or parenteral routes. Non-limiting parenteral routes of administration include subcutaneous, intramuscular, intraperitoneal, intravenous, transdermal, inhalation, intranasal, intra-arterial, intrathecal, enteral, sublingual, or rectal. Intravenous administration, for example, can be performed by injection of a unit dose. The term "unit dose" when used in reference to a pharmaceutical composition of the present invention refers to physically discrete units suitable as unitary dosage for humans, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required diluent; i.e., carrier, or vehicle.

In one particular embodiment of the present invention, the disclosed pharmaceutical compositions are administered via mucoactive aerosol therapy (see, e.g., M. Fuloria and B.K. Rubin, 2000, *Respir. Care* **45**:868-873; I. Gonda, 2000, *J. Pharm. Sci.* **89**:940-945; R. Dhand, 2000, *Curr. Opin. Pulm. Med.* **6**(1):59-70; B.K. Rubin, 2000, *Respir. Care* **45**(6):684-94; S. Suarez and A.J. Hickey, 2000, *Respir. Care* **45**(6):652-66).

Pharmaceutical compositions are administered in a manner compatible with the dosage formulation, and in a therapeutically effective amount. The quantity to be administered depends on the subject to be treated, capacity of the subject's immune system to utilize the active ingredient, and degree of modulation of Gene 216 activity desired. Precise amounts of active ingredient

required to be administered depend on the judgment of the practitioner and are specific for each individual. However, suitable dosages may range from about 0.1 to 20, preferably about 0.5 to about 10, and more preferably one to several, milligrams of active ingredient per kilogram body weight of individual per day and depend on the route of administration. Suitable regimes for initial administration and booster shots are also variable, but are typified by an initial administration followed by repeated doses at one or more hour intervals by a subsequent injection or other administration. Alternatively, continuous intravenous infusions sufficient to maintain concentrations of 10 nM to 10  $\mu$ M in the blood are contemplated. An exemplary pharmaceutical formulation comprises: Gene 216 antagonist or inhibitor (5.0 mg/ml); sodium bisulfite USP (3.2 mg/ml); disodium edetate USP (0.1 mg/ml); and water for injection q.s.a.d. (1.0 ml). As used herein, "pg" means picogram, "ng" means nanogram, " $\mu$ g" means microgram, "mg" means milligram, " $\mu$ l" means microliter, "ml" means milliliter, and "l" means L.

For further guidance in preparing pharmaceutical formulations, see, e.g., Gilman et al. (eds), 1990, *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, 8th ed., Pergamon Press; and *Remington's Pharmaceutical Sciences*, 17th ed., 1990, Mack Publishing Co., Easton, PA; Avis et al. (eds), 1993, *Pharmaceutical Dosage Forms: Parenteral Medications*, Dekker, New York; Lieberman et al. (eds), 1990, *Pharmaceutical Dosage Forms: Disperse Systems*, Dekker, New York.

**Pharmacogenetics:** The Gene 216 polypeptides and polynucleotides are also useful in pharmacogenetic analysis (i.e., the study of the relationship between an individual's genotype and that individual's response to a therapeutic composition or drug). See, e.g., M. Eichelbaum, 1996, *Clin. Exp. Pharmacol. Physiol.* **23**(10-11):983-985, and M.W. Linder, 1997, *Clin. Chem.* **43**(2):254-266. The genotype of the individual can determine the way a therapeutic acts on the body or the way the body metabolizes the therapeutic. Further, the activity of drug metabolizing enzymes affects both the intensity and duration of therapeutic activity. Differences in the activity or metabolism

of therapeutics can lead to severe toxicity or therapeutic failure. Accordingly, a physician or clinician may consider applying knowledge obtained in relevant pharmacogenetic studies in determining whether to administer a Gene 216 polypeptide, polynucleotide, analog, antagonist, inhibitor, or modulator, as well  
5 as tailoring the dosage and/or therapeutic or prophylactic treatment regimen.

In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions can be due to a single factor that alters the way the drug act on the body (altered drug action), or a factor that alters the way the body metabolizes the drug (altered drug metabolism). These  
10 conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited enzymopathy which results in haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

The discovery of genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These  
15 polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. The gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers quite frequently  
20 experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response. This has been demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. At the other extreme, ultra-rapid metabolizers fail to respond to standard doses. Recent  
25 studies have determined that ultra-rapid metabolism is attributable to CYP2D6 gene amplification.  
30

By analogy, genetic polymorphism or mutation may lead to allelic variants of Gene 216 in the population which have different levels of activity. The Gene 216 polypeptides or polynucleotides thereby allow a clinician to ascertain a genetic predisposition that can affect treatment modality. In addition, genetic mutation or variants at other genes may potentiate or diminish the activity of Gene 216-targeted drugs. Thus, in a Gene 216-based treatment, polymorphism or mutation may give rise to individuals that are more or less responsive to treatment. Accordingly, dosage would necessarily be modified to maximize the therapeutic effect within a given population containing the polymorphism. As an alternative to genotyping, specific polymorphic polypeptides or polynucleotides can be identified.

To identify genes that modify Gene 216-targeted drug response, several pharmacogenetic methods can be used. One pharmacogenomics approach, "genome-wide association", relies primarily on a high-resolution map of the human genome. This high-resolution map shows previously identified gene-related markers (e.g., a "bi-allelic" gene marker map which consists of 60,000-100,000 polymorphic or variable sites on the human genome, each of which has two variants). A high-resolution genetic map can then be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, a high-resolution map can be generated from a combination of some ten million known single nucleotide polymorphisms (SNPs) in the human genome. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In this way, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals (see, e.g., D.R. Pfost et al., 2000, *Trends Biotechnol.* **18**(8):334-8).

As another example, the "candidate gene approach", can be used. According to this method, if a gene that encodes a drug target is known, all

common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

As yet another example, a "gene expression profiling approach", can be used. This method involves testing the gene expression of an animal treated with a drug (e.g., a Gene 216 polypeptide, polynucleotide, analog, or modulator) to determine whether gene pathways related to toxicity have been turned on.

Information obtained from one of the approaches described herein can be used to establish a pharmacogenetic profile, which can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment an individual. A pharmacogenetic profile, when applied to dosing or drug selection, can be used to avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a Gene 216 polypeptide, polynucleotide, analog, antagonist, inhibitor, or modulator.

Gene 216 polypeptides or polynucleotides are also useful for monitoring therapeutic effects during clinical trials and other treatment. Thus, the therapeutic effectiveness of an agent that is designed to increase or decrease gene expression, polypeptide levels, or activity can be monitored over the course of treatment using the Gene 216 compositions or modulators. For example, monitoring can be performed by: 1) obtaining a pre-administration sample from a subject prior to administration of the agent; 2) detecting the level of expression or activity of the protein in the pre-administration sample; 3) obtaining one or more post-administration samples from the subject; 4) detecting the level of expression or activity of the polypeptide in the post-administration samples; 5) comparing the level of expression or activity of the polypeptide in the pre-administration sample with the polypeptide in the post-administration sample or samples; and 6) increasing or decreasing the administration of the agent to the subject accordingly.

Gene Therapy: In recent years, significant technological advances have



been made in the area of gene therapy for both genetic and acquired diseases (Kay et al., 1997, *Proc. Natl. Acad. Sci. USA*, **94**:12744-12746). Gene therapy can be defined as the transfer of DNA for therapeutic purposes. Improvement in gene transfer methods has allowed for development of gene therapy  
5 protocols for the treatment of diverse types of diseases. Gene therapy has also taken advantage of recent advances in the identification of new therapeutic genes, improvement in both viral and non-viral gene delivery systems, better understanding of gene regulation, and improvement in cell isolation and transplantation. Gene therapy would be carried out according to  
10 generally accepted methods as described by, for example, Friedman, 1991, *Therapy for Genetic Diseases*, Friedman, Ed., Oxford University Press, pages 105-121.

Vectors for introduction of genes both for recombination and for extrachromosomal maintenance are known in the art, and any suitable vector  
15 may be used. Methods for introducing DNA into cells such as electroporation, calcium phosphate co-precipitation, and viral transduction are known in the art, and the choice of method is within the competence of one skilled in the art (Robbins (ed), 1997, *Gene Therapy Protocols*, Human Press, NJ). Cells transformed with a Gene 216 gene can be used as model systems to study  
20 chromosome 20 disorders and to identify drug treatments for the treatment of such disorders.

Gene transfer systems known in the art may be useful in the practice of the gene therapy methods of the present invention. These include viral and non-viral transfer methods. A number of viruses have been used as gene  
25 transfer vectors, including polyoma, *i.e.*, SV40 (Madzak et al., 1992, *J. Gen. Virol.*, **73**:1533-1536), adenovirus (Berkner, 1992, *Curr. Top. Microbiol. Immunol.*, **158**:39-6; Berkner et al., 1988, *Bio Techniques*, **6**:616-629; Gorziglia et al., 1992, *J. Virol.*, **66**:4407-4412; Quantin et al., 1992, *Proc. Natl. Acad. Sci. USA*, **89**:2581-2584; Rosenfeld et al., 1992, *Cell*, **68**:143-155; Wilkinson et al.,  
30 1992, *Nucl. Acids Res.*, **20**:2233-2239; Stratford-Perricaudet et al., 1990, *Hum. Gene Ther.*, **1**:241-256), vaccinia virus (Mackett et al., 1992, *Biotechnology*,

24:495- 499), adeno-associated virus (Muzyczka, 1992, *Curr. Top. Microbiol. Immunol.*, **158**:91- 123; Ohi et al., 1990, *Gene*, **89**:279-282), herpes viruses including HSV and EBV (Margolskee, 1992, *Curr. Top. Microbiol. Immunol.*, **158**:67-90; Johnson et al., 1992, *J. Virol.*, **66**:2952-2965; Fink et al., 1992, 5 *Hum. Gene Ther.*, **3**:11-19; Breakfield et al., 1987, *Mol. Neurobiol.*, **1**:337-371; Fresse et al., 1990, *Biochem. Pharmacol.*, **40**:2189-2199), and retroviruses of avian (Brandyopadhyay et al., 1984, *Mol. Cell Biol.*, **4**:749-754; Petropoulos et al., 1992, *J. Virol.*, **66**:3391-3397), murine (Miller, 1992, *Curr. Top. Microbiol. Immunol.*, **158**:1-24; Miller et al., 1985, *Mol. Cell Biol.*, **5**:431-437; Sorge et al., 10 1984, *Mol. Cell Biol.*, **4**:1730-1737; Mann et al., 1985, *J. Virol.*, **54**:401- 407), and human origin (Page et al., 1990, *J. Virol.*, **64**:5370-5276; Buchschalcher et al., 1992, *J. Virol.*, **66**:2731-2739). Most human gene therapy protocols have been based on disabled murine retroviruses.

Non-viral gene transfer methods known in the art include chemical 15 techniques such as calcium phosphate coprecipitation (Graham et al., 1973, *Virology*, **52**:456-467; Pellicer et al., 1980, *Science*, **209**:1414-1422), mechanical techniques, for example microinjection (Anderson et al., 1980, *Proc. Natl. Acad. Sci. USA*, **77**:5399-5403; Gordon et al., 1980, *Proc. Natl. Acad. Sci. USA*, **77**:7380-7384; Brinster et al., 1981, *Cell*, **27**:223-231; 20 Constantini et al., 1981, *Nature*, **294**:92-94), membrane fusion-mediated transfer via liposomes (Felgner et al., 1987, *Proc. Natl. Acad. Sci. USA*, **84**:7413-7417; Wang et al., 1989, *Biochemistry*, **28**:9508-9514; Kaneda et al., 1989, *J. Biol. Chem.*, **264**:12126-12129; Stewart et al., 1992, *Hum. Gene Ther.*, **3**:267-275; Nabel et al., 1990, *Science*, **249**:1285-1288; Lim et al., 1992, 25 *Circulation*, **83**:2007-2011), and direct DNA uptake and receptor-mediated DNA transfer (Wolff et al., 1990, *Science*, **247**:1465-1468; Wu et al., 1991, *BioTechniques*, **11**:474-485; Zenke et al., 1990, *Proc. Natl. Acad. Sci. USA*, **87**:3655-3659; Wu et al., 1989, *J. Biol. Chem.*, **264**:16985-16987; Wolff et al., 1991, *BioTechniques*, **11**:474-485; Wagner et al., 1991, *Proc. Natl. Acad. Sci. USA*, **88**:4255-4259; Cotten et al., 1990, *Proc. Natl. Acad. Sci. USA*, **87**:4033- 30

4037; Curiel et al., 1991, *Proc. Natl. Acad. Sci. USA*, **88**:8850-8854; Curiel et al., 1991, *Hum. Gene Ther.*, **3**:147-154).

In one approach, plasmid DNA is complexed with a polylysine-conjugated antibody specific to the adenovirus hexon protein, and the resulting  
5 complex is bound to an adenovirus vector. The trimolecular complex is then used to infect cells. The adenovirus vector permits efficient binding, internalization, and degradation of the endosome before the coupled DNA is damaged.

In another approach, liposome/DNA is used to mediate direct *in vivo*  
10 gene transfer. While in standard liposome preparations the gene transfer process is non-specific, localized *in vivo* uptake and expression have been reported in tumor deposits, for example, following direct *in situ* administration (Nabel, 1992, *Hum. Gene Ther.*, **3**:399-410).

Suitable gene transfer vectors possess a promoter sequence, preferably  
15 a promoter that is cell-specific and placed upstream of the sequence to be expressed. The vectors may also contain, optionally, one or more expressible marker genes for expression as an indication of successful transfection and expression of the nucleic acid sequences contained in the vector. In addition, vectors can be optimized to minimize undesired immunogenicity and maximize  
20 long-term expression of the desired gene product(s) (see Nabe, 1999, *Proc. Natl. Acad. Sci. USA* **96**:324-326). Moreover, vectors can be chosen based on cell-type that is targeted for treatment. Notably, gene transfer therapies have been initiated for the treatment of various pulmonary diseases (see, e.g., M.J. Welsh, 1999, *J. Clin. Invest.* **104**(9):1165-6; D.L. Ennist, 1999, *Trends Pharmacol. Sci.* **20**:260-266; S.M. Albelda et al., 2000, *Ann. Intern. Med.* **132**:649-660; E. Alton and C. Kitson C., 2000, *Expert Opin. Investig. Drugs.* **9**(7):1523-35).

Illustrative examples of vehicles or vector constructs for transfection or  
infection of the host cells include replication-defective viral vectors, DNA virus  
30 or RNA virus (retrovirus) vectors, such as adenovirus, herpes simplex virus and adeno-associated viral vectors. Adeno-associated virus vectors are single

stranded and allow the efficient delivery of multiple copies of nucleic acid to the cell's nucleus. Preferred are adenovirus vectors. The vectors will normally be substantially free of any prokaryotic DNA and may comprise a number of different functional nucleic acid sequences. An example of such functional sequences may be a DNA region comprising transcriptional and translational initiation and termination regulatory sequences, including promoters (e.g., strong promoters, inducible promoters, and the like) and enhancers which are active in the host cells. Also included as part of the functional sequences is an open reading frame (polynucleotide sequence) encoding a protein of interest.

Flanking sequences may also be included for site-directed integration. In some situations, the 5'-flanking sequence will allow homologous recombination, thus changing the nature of the transcriptional initiation region, so as to provide for inducible or non-inducible transcription to increase or decrease the level of transcription, as an example.

In general, the encoded and expressed Gene 216 polypeptide may be intracellular, i.e., retained in the cytoplasm, nucleus, or in an organelle, or may be secreted by the cell. For secretion, the natural signal sequence present in Gene 216 may be retained. When the polypeptide or peptide is a fragment of a Gene 216 protein, a signal sequence may be provided so that, upon secretion and processing at the processing site, the desired protein will have the natural sequence. Specific examples of coding sequences of interest for use in accordance with the present invention include the Gene polypeptide coding sequences, e.g., SEQ ID NO:4.

As previously mentioned, a marker may be present for selection of cells containing the vector construct. The marker may be an inducible or non-inducible gene and will generally allow for positive selection under induction, or without induction, respectively. Examples of marker genes include neomycin, dihydrofolate reductase, glutamine synthetase, and the like. The vector employed will generally also include an origin of replication and other genes that are necessary for replication in the host cells, as routinely employed by those having skill in the art. As an example, the replication system

comprising the origin of replication and any proteins associated with replication encoded by a particular virus may be included as part of the construct. The replication system must be selected so that the genes encoding products necessary for replication do not ultimately transform the cells. Such replication systems are represented by replication-defective adenovirus (see G. Acsadi et al., 1994, *Hum. Mol. Genet.* **3**:579-584) and by Epstein-Barr virus. Examples of replication defective vectors, particularly, retroviral vectors that are replication defective, are BAG, (see Price et al., 1987, *Proc. Natl. Acad. Sci. USA*, **84**:156; Sanes et al., 1986, *EMBO J.*, **5**:3133). It will be understood that the final gene construct may contain one or more genes of interest, for example, a gene encoding a bioactive metabolic molecule. In addition, cDNA, synthetically produced DNA or chromosomal DNA may be employed utilizing methods and protocols known and practiced by those having skill in the art.

According to one approach for gene therapy, a vector encoding a Gene 216 polypeptide is directly injected into the recipient cells (*in vivo* gene therapy). Alternatively, cells from the intended recipients are explanted, genetically modified to encode a Gene 216 polypeptide, and reimplanted into the donor (*ex vivo* gene therapy). An *ex vivo* approach provides the advantage of efficient viral gene transfer, which is superior to *in vivo* gene transfer approaches. In accordance with *ex vivo* gene therapy, the host cells are first transfected with engineered vectors containing at least one gene encoding a Gene 216 polypeptide, suspended in a physiologically acceptable carrier or excipient such as saline or phosphate buffered saline, and the like, and then administered to the host. The desired gene product is expressed by the injected cells, which thus introduce the gene product into the host. The introduced gene products can thereby be utilized to treat or ameliorate a disorder that is related to altered levels of Gene 216 (e.g., asthma).

#### **Animal Models**

Gene 216 polynucleotides can be used to generate genetically altered non-human animals or human cell lines. Any non-human animal can be used; however typical animals are rodents, such as mice, rats, or guinea pigs.

Genetically engineered animals or cell lines can carry a gene that has been altered to contain deletions, substitutions, insertions, or modifications of the polynucleotide sequence (e.g., exon sequence). Such alterations may render the gene nonfunctional, (i.e., a null mutation) producing a "knockout" animal or cell line. In addition, genetically engineered animals can carry one or more exogenous or non-naturally occurring genes, i.e., "transgenes", that are derived from different organisms (e.g., humans), or produced by synthetic or recombinant methods. Genetically altered animals or cell lines can be used to study Gene 216 function, regulation, and treatments for Gene 216-related diseases. In particular, knockout animals and cell lines can be used to establish animal models and *in vitro* models for Gene 216-related illnesses, respectively. In addition, transgenic animals expressing human Gene 216 can be used in drug discovery efforts.

A "transgenic animal" is any animal containing one or more cells bearing genetic information altered or received, directly or indirectly, by deliberate genetic manipulation at a subcellular level, such as by targeted recombination or microinjection or infection with recombinant virus. The term "transgenic animal" is not intended to encompass classical cross-breeding or *in vitro* fertilization, but rather is meant to encompass animals in which one or more cells are altered by, or receive, a recombinant DNA molecule. This recombinant DNA molecule may be specifically targeted to a defined genetic locus, may be randomly integrated within a chromosome, or it may be extrachromosomally replicating DNA.

Transgenic animals can be selected after treatment of germline cells or zygotes. For example, expression of an exogenous Gene 216 gene or a variant can be achieved by operably linking the gene to a promoter and optionally an enhancer, and then microinjecting the construct into a zygote (see, e.g., Hogan et al., *Manipulating the Mouse Embryo, A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY). Such treatments include insertion of the exogenous gene and disrupted homologous genes. Alternatively, the gene(s) of the animals may be disrupted by insertion

or deletion mutation of other genetic alterations using conventional techniques (see, e.g., Capecchi, 1989, *Science*, **244**:1288; Valancuis et al., 1991, *Mol. Cell Biol.*, **11**:1402; Hasty et al., 1991, *Nature*, **350**:243; Shinkai et al., 1992, *Cell*, **68**:855; Mombaerts et al., 1992, *Cell*, **68**:869; Philpott et al., 1992, *Science*, **256**:1448; Snouwaert et al., 1992, *Science*, **257**:1083; Donehower et al., 1992, *Nature*, **356**:215).

In one aspect of the invention, Gene 216 knockout mice can be produced in accordance with well-known methods (see, e.g., M.R. Capecchi, 1989, *Science*, **244**:1288-1292; P. Li et al., 1995, *Cell* **80**:401-411; L.A. Galli-  
10 Taliadoros et al., 1995, *J. Immunol. Methods* **181**(1):1-15; C.H. Westphal et al., 1997, *Curr. Biol.* **7**(7):530-3; S.S. Cheah et al., 2000, *Methods Mol. Biol.* **136**:455-63). The disclosed murine Gene 216 genomic clone can be used to prepare a Gene 216 targeting construct that can disrupt Gene 216 in the mouse by homologous recombination at the Gene 216 chromosomal locus.  
15 The targeting construct can comprise a disrupted or deleted Gene 216 sequence that inserts in place of the functioning portion of the native mouse gene. For example, the construct can contain an insertion in the Gene 216 protein-coding region.

Preferably, the targeting construct contains markers for both positive  
20 and negative selection. The positive selection marker allows the selective elimination of cells that lack the marker, while the negative selection marker allows the elimination of cells that carry the marker. In particular, the positive selectable marker can be an antibiotic resistance gene, such as the neomycin resistance gene, which can be placed within the coding sequence of Gene 216  
25 to render it non-functional, while at the same time rendering the construct selectable. The herpes simplex virus thymidine kinase (HSV tk) gene is an example of a negative selectable marker that can be used as a second marker to eliminate cells that carry it. Cells with the HSV tk gene are selectively killed in the presence of gangcyclovir. As an example, a positive selection marker  
30 can be positioned on a targeting construct within the region of the construct that integrates at the Gene 216 locus. The negative selection marker can be

positioned on the targeting construct outside the region that integrates at the Gene 216 locus. Thus, if the entire construct is present in the cell, both positive and negative selection markers will be present. If the construct has integrated into the genome, the positive selection marker will be present, but  
5 the negative selection marker will be lost.

The targeting construct can be employed, for example, in embryonal stem cell (ES). ES cells may be obtained from pre-implantation embryos cultured *in vitro* (M.J. Evans et al., 1981, *Nature* **292**:154-156; M.O. Bradley et al., 1984, *Nature* **309**:255-258; Gossler et al., 1986, *Proc. Natl. Acad. Sci. USA*  
10 **83**:9065-9069; Robertson et al., 1986, *Nature* **322**:445-448; S. A. Wood et al., 1993, *Proc. Natl. Acad. Sci. USA* **90**:4582-4584). Targeting constructs can be efficiently introduced into the ES cells by standard techniques such as DNA transfection or by retrovirus-mediated transduction. Following this, the transformed ES cells can be combined with blastocysts from a non-human  
15 animal. The introduced ES cells colonize the embryo and contribute to the germ line of the resulting chimeric animal (R. Jaenisch, 1988, *Science* **240**:1468-1474). The use of gene-targeted ES cells in the generation of gene-targeted transgenic mice has been previously described (Thomas et al., 1987, *Cell* **51**:503-512) and is reviewed elsewhere (Frohman et al., 1989, *Cell*  
20 **56**:145-147; Capecchi, 1989, *Trends in Genet.* **5**:70-76; Baribault et al., 1989, *Mol. Biol. Med.* **6**:481-492; Wagner, 1990, *EMBO J.* **9**:3025-3032; Bradley et al., 1992, *Bio/Technology* **10**: 534-539).

Several methods can be used to select homologously recombined murine ES cells. One method employs PCR to screen pools of transformant  
25 cells for homologous insertion, followed by screening individual clones (Kim et al., 1988, *Nucleic Acids Res.* **16**:8887-8903; Kim et al., 1991, *Gene* **103**:227-233). Another method employs a marker gene is constructed which will only be active if homologous insertion occurs, allowing these recombinants to be selected directly (Sedivy et al., 1989, *Proc. Natl. Acad. Sci. USA* **86**:227-231).  
30 For example, the positive-negative selection (PNS) method can be used as described above (see, e.g., Mansour et al., 1988, *Nature* **336**:348-352;



Capecchi, 1989, *Science* **244**:1288-1292; Capecchi, 1989, *Trends in Genet.* **5**:70-76). In particular, the PNS method is useful for targeting genes that are expressed at low levels.

The absence of functional Gene 216 in the knockout mice can be confirmed, for example, by RNA analysis, protein expression analysis, and functional studies. For RNA analysis, RNA samples are prepared from different organs of the knockout mice and the Gene 216 transcript is detected in Northern blots using oligonucleotide probes specific for the transcript. For protein expression detection, antibodies that are specific for the Gene 216 polypeptide are used, for example, in flow cytometric analysis, immunohistochemical staining, and activity assays. Alternatively, functional assays are performed using preparations of different cell types collected from the knockout mice.

Several approaches can be used to produce transgenic mice. In one approach, a targeting vector is integrated into ES cell by homologous recombination, an intrachromosomal recombination event is used to eliminate the selectable markers, and only the transgene is left behind (A.L. Joyner et al., 1989, *Nature* **338**(6211):153-6; P. Hasty et al., 1991, *Nature* **350**(6315):243-6; V. Valancius and O. Smithies, 1991, *Mol. Cell Biol.* **11**(3):1402-8; S. Fiering et al., 1993, *Proc. Natl. Acad. Sci. USA* **90**(18):8469-73). In an alternative approach, two or more strains are created; one strain contains the gene knocked-out by homologous recombination, while one or more strains contain transgenes. The knockout strain is crossed with the transgenic strain to produce new line of animals in which the original wild-type allele has been replaced (although not at the same site) with a transgene. Notably, knockout and transgenic animals can be produced by commercial facilities (e.g., The Lerner Research Institute, Cleveland, OH; B&K Universal, Inc., Fremont, CA; DNX Transgenic Sciences, Cranbury, NJ; Incyte Genomics, Inc., St. Louis, MO).

Transgenic animals (e.g., mice) containing a nucleic acid molecule which encodes human Gene 216, may be used as *in vivo* models to study the

overexpression of Gene 216. Such animals can also be used in drug evaluation and discovery efforts to find compounds effective to inhibit or modulate the activity of Gene 216, such as for example compounds for treating respiratory disorders, diseases, or conditions. One having ordinary skill in the art can use standard techniques to produce transgenic animals which produce human Gene 216 polypeptide, and use the animals in drug evaluation and discovery projects (see, e.g., U.S. Patent No. 4,873,191 to Wagner; U.S. Patent No. 4,736,866 to Leder).

In another embodiment of the present invention, the transgenic animal can comprise a recombinant expression vector in which the nucleotide sequence that encodes human Gene 216 is operably linked to a tissue specific promoter whereby the coding sequence is only expressed in that specific tissue. For example, the tissue specific promoter can be a mammary cell specific promoter and the recombinant protein so expressed is recovered from the animal's milk.

In yet another embodiment of the present invention, a Gene 216 "knockout" can be produced by administering to the animal antibodies (e.g., neutralizing antibodies) that specifically recognize an endogenous Gene 216 polypeptide. The antibodies can act to disrupt function of the endogenous Gene 216 polypeptide, and thereby produce a null phenotype. In one specific example, an orthologous mouse Gene 216 polypeptide (e.g., SEQ ID NO:366) or peptide can be used to generate antibodies. These antibodies can be given to a mouse to knockout the function of the mouse Gene 216 ortholog.

In addition, non-mammalian organisms may be used to study Gene 216 and Gene 216-related diseases. For example, model organisms such as *C. elegans*, *D. melanogaster*, and *S. cerevisiae* may be used. Gene 216 homologues can be identified in these model organisms, and mutated or deleted to produce a Gene 216-deficient strain. Human Gene 216 can then be tested for the ability to "complement" the Gene 216-deficient strain. Gene 216-deficient strains can also be used for drug screening. The study of Gene 216 homologs can facilitate the understanding of human Gene 216 biological

function, and assist in the identification of binding proteins (e.g., agonists and antagonists).

### **Gene Identification**

To identify genes in the region on 20p13-p12, a set of bacterial artificial  
5 chromosome(BAC) clones containing this chromosomal region was identified  
in accordance with the methods described herein. The BAC clones served as  
a template for genomic DNA sequencing and served as reagents for identifying  
coding sequences by direct cDNA selection. Genomic sequencing and direct  
cDNA selection methods were used to characterize DNA from 20p13-p12.

10 When one or more genes have been genetically localized to a specific  
chromosomal region, the gene(s) can be characterized at the molecular level  
by a series of steps that include: 1) cloning the entire region of DNA in a set  
of overlapping clones (physical mapping); 2) characterizing the gene(s)  
15 encoded by these clones by a combination of direct cDNA selection, exon  
trapping and DNA sequencing (gene identification); and 3) identifying  
mutations (i.e., SNPs) in the gene(s) by comparative DNA sequencing of  
affected and unaffected members of the kindred and/or in unrelated affected  
individuals and unrelated unaffected controls (mutation analysis).

Physical mapping is accomplished by screening libraries of human DNA  
20 cloned in vectors that are propagated in a host such as *E. coli*, using  
hybridization or PCR assays from unique molecular landmarks in the  
chromosomal region of interest. In accordance with the present invention, a  
physical map of the disorder region was generated by screening a library of  
human DNA cloned in BACs with a set overgo markers that had been  
25 previously mapped to chromosome 20p13-p12 by the efforts of the Human  
Genome Project. Overgos are unique molecular landmarks in the human  
genome that can be assayed by hybridization. The location of thousands of  
overgos on the twenty-two autosomes and two sex chromosomes has been  
determined through the efforts of the Human Genome Project. For a positional  
30 cloning effort, the physical map is tied to the genetic map because the markers  
used for genetic mapping can also be used as overgos for physical mapping.

By screening a BAC library with a combination of overgos derived from genetic markers, genes, and random DNA fragments, a physical map comprised of overlapping clones representing all of the DNA in a chromosomal region of interest can be assembled.

5           BACs are cloning vectors for large (80 kilobase to 200 kilobase) segments of human or other DNA that are propagated in *E. coli*. To construct a physical map using BACs, a library of BAC clones is screened so that individual clones harboring the DNA sequence corresponding to a given overgo or set of overgos are identified. Throughout most of the human genome, the  
10           overgo markers are spaced approximately 20 to 50 kilobases apart, so that an individual BAC clone typically contains at least two overgo markers. In addition, the BAC libraries that were screened contain enough cloned DNA to cover the human genome twelve times over. An individual overgo typically identifies more than one BAC clone. By screening a twelve-fold coverage BAC  
15           library with a series of overgo markers spaced approximately 50 kilobases apart, a physical map consisting of a series of overlapping contiguous BAC clones, i.e., BAC "contigs," can be assembled for any region of the human genome. This map is closely tied to the genetic map because many of the overgo markers used to prepare the physical map are also genetic markers.

20           When constructing a physical map, it often happens that there are gaps in the overgo map of the genome that result in the inability to identify BAC clones that are overlapping in a given location. Typically, the physical map is first constructed from a set of overgos identified through the publicly available literature and World Wide Web resources. The initial map consists of several  
25           separate BAC contigs that are separated by gaps of unknown molecular distance. To identify BAC clones that fill these gaps, it is necessary to develop new overgo markers from the ends of the clones on either side of the gap. This is done by sequencing the terminal 200 to 300 base pairs of the BACs flanking the gap, and developing a PCR or hybridization based assay. If the  
30           terminal sequences are demonstrated to be unique within the human genome, then the new overgo can be used to screen the BAC library to identify

additional BACs that contain the DNA from the gap in the physical map. To assemble a BAC contig that covers a region the size of the disorder region (6,000,000 or more base pairs), it is necessary to develop new overgo markers from the ends of a number of clones.

5           After building a BAC contig, this set of overlapping clones serves as a template for identifying the genes encoded in the chromosomal region. Gene identification can be accomplished by many methods. Three methods are commonly used: 1) a set of BACs selected from the BAC contig to represent the entire chromosomal region are sequenced, and computational methods are  
10       used to identify all of the genes; 2) the BACs from the BAC contig are used as a reagent to clone cDNAs corresponding to the genes encoded in the region by a method termed direct cDNA selection; or 3) the BACs from the BAC contig are used to identify coding sequences by selecting for specific DNA sequence motifs in a procedure called exon trapping. Gene 216 was identified by  
15       methods (1) and (2) in accordance with the techniques disclosed herein.

          To sequence the entire BAC contig representing the disorder region, a set of BACs can be chosen for subcloning into plasmid vectors and subsequent DNA sequencing of these subclones. Since the DNA cloned in the BACs represents genomic DNA, this sequencing is referred to as genomic  
20       sequencing to distinguish it from cDNA sequencing. To initiate the genomic sequencing for a chromosomal region of interest, several non-overlapping BAC clones are chosen. DNA for each BAC clone is prepared, and the clones are sheared into random small fragments that are subsequently cloned into standard plasmid vectors such as pUC18. The plasmid clones are then grown  
25       to propagate the smaller fragments, and these are the templates for sequencing. To ensure adequate coverage and sequence quality for the BAC DNA sequence, sufficient plasmid clones are sequenced to yield three-fold coverage of the BAC clone. For example, if the BAC is 100 kilobases long, then phagemids are sequenced to yield 300 kilobases of sequence. Since the  
30       BAC DNA is randomly sheared prior to cloning in the phagemid vector, the 300 kilobases of raw DNA sequence can be assembled by computational methods

into overlapping DNA sequences termed sequence contigs. For the purposes of initial gene identification by computational methods, three-fold coverage of each BAC is sufficient to yield twenty to forty sequence contigs of 1000 base pairs to 20,000 base pairs.

5 In accordance with the present invention, the "seed" BACs from the BAC contig in the disorder region were sequenced. The sequence of the "seed" BACs was then used to identify minimally overlapping BACs from the contig, and these were subsequently sequenced. In this manner, the entire candidate region can be sequenced, with several small sequence gaps left in  
10 each BAC. This sequence serves as the template for computational gene identification. In one approach, genes can be identified by comparing the sequence of BAC contig to publicly available databases of cDNA and genomic sequences, e.g. UniGene, dbEST, EMBL nucleotide database, GenBank, and the DNA Database of Japan (DDBJ). The BAC DNA sequence can also be  
15 translated into protein sequence, and the protein sequence can be used to search publicly available protein databases, e.g., GenPept, EMBL protein database, Protein Information Resource (PIR), Protein Data Bank (PDB), and SWISS-PROT. These comparisons are typically done using the BLAST family of computer algorithms and programs (Altschul et al., 1990, *J. Mol. Biol.*,  
20 215:403-410; Altschul et al, 1997, *Nucl. Acids Res.*, **25**:3389-3402).

For nucleotide queries, BLASTN, BLASTX, and TBLASTX can be used. BLASTN compares a nucleotide query sequence with a nucleotide sequence database; BLASTX compares a nucleotide query sequence translated in all reading frames against a protein sequence database; TBLASTX compares the  
25 six-frame translations of a nucleotide query sequence against the six-frame translations of a nucleotide sequence database. For protein queries, BLASTP and TBLASTN can be used. BLASTP compares a protein query sequence with a protein sequence database; TBLASTN compares a protein query sequence against a nucleotide sequence database dynamically translated in  
30 all reading frames.

Additionally, computer algorithms such as MZEF (Zhang, 1997, *Proc.*

*Natl. Acad. Sci. USA* **94**:565-568), GRAIL (Uberbacher et al., 1996, *Methods Enzymol.*, **266**:259-281), and Genscan (Burge and Karlin, 1997, *J. Mol. Biol.*, **268**:78-94) can be used to predict the location of exons in the sequence based on the presence of specific DNA sequence motifs that are common to all  
5 exons, as well as the presence of codon usage typical of human protein encoding sequences.

In addition to identifying genes by computational methods, genes can be identified by direct cDNA selection (Del Mastro and Lovett, 1996, *Methods in Molecular Biology*, Humana Press Inc., NJ). In direct cDNA selection, cDNA  
10 pools from tissues of interest are prepared, and BACs from the candidate region are used in a liquid hybridization assay to capture the cDNAs which base pair to coding regions in the BAC. In the methods described herein, the cDNA pools were created from several different tissues by random priming and oligo dT priming the first strand cDNA from poly A<sup>+</sup> RNA, synthesizing the  
15 second-strand cDNA by standard methods, and adding linkers to the ends of the cDNA fragments. In this approach, the linkers are used to amplify the cDNA pools of BAC clones from the disorder region identified by screening a BAC library. The amplified products are then used as a template for initiating DNA synthesis to create a biotin labeled copy of BAC DNA. Following this, the  
20 biotin labeled copy of the BAC DNA is denatured and incubated with an excess of the PCR amplified, linkered cDNA pools which have also been denatured. The BAC DNA and cDNA are allowed to anneal in solution, and heteroduplexes between the BAC and the cDNA are isolated using streptavidin coated magnetic beads. The cDNAs that are captured by the BAC are then  
25 amplified using primers complimentary to the linker sequences, and the hybridization/selection process is repeated for a second round. After two rounds of direct cDNA selection, the cDNA fragments are cloned, and a library of these direct selected fragments is created.

The cDNA clones isolated by direct selection are analyzed by two  
30 methods. Where the genomic target DNA sequence is obtained from a pool of BACs from the disorder region, the cDNAs are mapped to BAC genomic

clones to verify their chromosomal location. This is accomplished by arraying the cDNAs in microtiter dishes, and replicating their DNA in high-density grids.

Individual genomic clones known to map to the region are then hybridized to the grid to identify direct selected cDNAs mapping to that region. cDNA clones  
5 that are confirmed to correspond to individual BACs are sequenced. To determine whether the cDNA clones isolated by direct selection share sequence identity or similarity to previously identified genes, the DNA and protein coding sequences are compared to publicly available databases using the BLAST family of programs described above.

10 The combination of genomic DNA sequence and cDNA sequence provided by BAC sequencing and by direct cDNA selection yields an initial list of putative genes in the region. In the present invention, the genes in the region were candidates for the asthma locus. To further characterize each gene, Northern blots were performed to determine the size of the transcript  
15 corresponding to each gene, and to determine which putative exons were transcribed together to make an individual gene. For Northern blot analysis of each gene, probes are prepared from direct selected cDNA clones or by PCR amplifying specific fragments from genomic DNA, cDNA or from the BAC encoding the putative gene of interest. The Northern blot analysis is used to  
20 determine the size of the transcript and the tissues in which it is expressed. For transcripts that are not highly expressed, it is sometimes necessary to perform a reverse transcription PCR assay using RNA from the tissues of interest as a template for the reaction.

Gene identification by computational methods and by direct cDNA  
25 selection provides unique information about the genes in a region of a chromosome. Once genes are identified, it is possible to examine subjects for sequence variants. Variant sequences can be inherited as allelic differences or can arise from spontaneous mutations.

Inherited alleles can be analyzed for linkage to a disease susceptibility  
30 locus. Linkage analysis is possible because of the nature of inheritance of chromosomes from parents to offspring. During meiosis, the two parental



homologs pair to guide their proper separation to daughter cells. While they are paired, the two homologs exchange pieces of the chromosomes, in an event called "crossing over" or "recombination." The resulting chromosomes contain parts that originate from both parental homologs. The closer together  
5 two sequences are on the chromosome, the less likely that a recombination event will occur between them, and the more closely linked they are.

In the present invention, data obtained from the different families were combined and analyzed together by a computer using statistical methods described herein. The results were then used as evidence for linkage between  
10 the genetic markers used and an asthma susceptibility locus.

In general, a recombination frequency of 1% is equivalent to approximately 1 map unit, a relationship that holds up to frequencies of about 20% or 20 cM. One centimorgan (cM) is roughly equivalent to 1,000 kb of DNA. The entire human genome is 3,300 cM long. In order to find an  
15 unknown disease gene within 5-10 cM of a marker locus, the whole human genome can be searched with roughly 330 informative marker loci spaced at approximately 10 cM intervals (Botstein et al., 1980, *Am. J. Hum. Genet.*, **32**:314-331).

The reliability of linkage results is established by using a number of  
20 statistical methods. The methods most commonly used for the detection by linkage analysis of oligogenes involved in the etiology of a complex trait are non-parametric or model-free methods which have been implemented into the computer programs MAPMAKER/SIBS (L. Kruglyak and E.S. Lander, 1995, *Am. J. Hum. Genet.* **57**:439-454) and GENEHUNTER (L. Kruglyak et al., 1996,  
25 *Am. J. Hum. Genet.* **58**:1347-1363). Typically, linkage analysis is performed by typing members of families with multiple affected individuals at a given marker locus and evaluating if the affected members (excluding parent-offspring pairs) share alleles at the marker locus that are identical by descent (IBD) more often than expected by chance alone.

30 As a result of the rapid advances in mapping the human genome over the last few years, and concomitant improvements in computer methodology,

it has become feasible to carry out linkage analyses using multi-point data. Multi-point analysis provides a simultaneous analysis of linkage between the trait and several linked genetic markers, when the recombination distance among the markers is known. A LOD score statistic is computed at multiple  
5 locations along a chromosome to measure the evidence that a susceptibility locus is located nearby. A LOD score is the logarithm base 10 of the ratio of the likelihood that a susceptibility locus exists at a given location to the likelihood that no susceptibility locus is located there. By convention, when testing a single marker, a total LOD score greater than +3.0 (that is, odds of  
10 linkage being 1,000 times greater than odds of no linkage) is considered to be significant evidence for linkage.

Multi-point analysis is advantageous for two reasons. First, the informativeness of the pedigrees is usually increased. Each pedigree has a certain amount of potential information, dependent on the number of parents  
15 heterozygous for the marker loci and the number of affected individuals in the family. However, few markers are sufficiently polymorphic as to be informative in all those individuals. If multiple markers are considered simultaneously, then the probability of an individual being heterozygous for at least one of the markers is greatly increased. Second, an indication of the position of the  
20 disease gene among the markers may be determined. This allows identification of flanking markers, and thus eventually allows identification of a small region in which the disease gene resides.

### **EXAMPLES**

The examples as set forth herein are meant to exemplify the various aspects of the present invention and are not intended to limit the invention in any way.

#### **5    EXAMPLE 1: Family Collection**

Asthma is a complex disorder that is influenced by a variety of factors, including both genetic and environmental effects. Complex disorders are typically caused by multiple interacting genes, some contributing to disease development and some conferring a protective effect. The success of linkage  
10    analyses in identifying chromosomes with significant LOD scores is achieved in part as a result of an experimental design tailored to the detection of susceptibility genes in complex diseases, even in the presence of epistasis and genetic heterogeneity. Also important are rigorous efforts in ascertaining asthmatic families that meet strict guidelines, and collecting accurate clinical  
15    information.

Given the complex nature of the asthma phenotype, non-parametric affected sib pair analyses were used to analyze the genetic data. This approach does not require parameter specifications such as mode of inheritance, disease allele frequency, penetrance of the disorder, or phenocopy  
20    rates. Instead, it determines whether the inheritance pattern of a chromosomal region is consistent with random segregation. Where segregation is not random, affected sibs inherit identical copies of alleles more often than expected by chance. Because no models for inheritance are assumed, allele-sharing methods tend to be more robust than parametric methods when  
25    analyzing complex disorders. They do, however, require larger sample sizes to reach statistically significant results.

At the outset of the program, the goal was to collect 400 affected sib-pair families for the linkage analyses. Based on a genome scan with markers spaced ~10 cM apart, this number of families was predicted to provide > 95%  
30    power to detect an asthma susceptibility gene that caused an increased risk to first-degree relatives of 3-fold or greater. The assumed relative risk of 3-fold

was consistent with epidemiological studies in the literature that suggest an increased risk ranging from 3- to 7-fold. The relative risk was based on gender, different classifications of the asthma phenotype (i.e. bronchial hyper-responsiveness versus physician's diagnosis) and, in the case of offspring, whether one or both parents were asthmatic.

The family collection efforts exceeded the initial goal of 400, obtaining a total of 444 affected sibling pair (ASP) families, with 342 families from the UK and 102 families from the US. The ASP families in the US collection were Caucasian with a minimum of two affected siblings that were identified through both private practice and community physicians as well as through advertising. A total of 102 families were collected in Kansas, Nebraska, and Southern California. In the UK collection, Caucasian families with a minimum of two affected siblings were identified through physicians' registers in a region surrounding Southampton and including the Isle of Wight. In both the US and UK collections, additional affected and unaffected sibs were collected whenever possible. An additional 39 families from the United Kingdom were utilized from an earlier collection effort with different ascertainment criteria. These families were recruited either: 1) without reference to asthma and atopy; or 2) by having at least one family member or at least two family members affected with asthma. The randomly ascertained samples were identified from general practitioner registers in the Southampton area. For families with affected members, the probands (i.e., the initial affected individuals identified) were recruited from hospital based clinics in Southampton. Seven pedigrees extended beyond a single nuclear family.

Families were included in the study if they met all of the following criteria: 1) the biological mother and biological father were Caucasian and agreed to participate in the study; 2) at least two biological siblings were alive, each with a current physician diagnosis of asthma, and were 5 to 21 years of age; and 3) the two siblings were currently taking asthma medications on a regular basis. This included regular, intermittent use of inhaled or oral bronchodilators and regular use of cromolyn, theophylline, or steroids.

Families were excluded from the study if they met any one of the following criteria: 1) both parents were affected (i.e., with a current diagnosis of asthma, having asthma symptoms, or on asthma medications at the time of the study); 2) any asthmatic family member to be included in the study was taking beta-blockers at the time of the study, 3) any family member to be included in the study had congenital or acquired pulmonary disease at birth (e.g. cystic fibrosis), a history of serious cardiac disease (myocardial infarction) or any history of serious pulmonary disease (e.g. emphysema); or 4) any family member to be included in the study was pregnant.

An extensive clinical instrument was designed and data from all participating family members were collected. The case report form (CRF) included questions on demographics, medical history including medications, a health survey on the incidence and frequency of asthma, wheeze, eczema, hay fever, nasal problems, smoking, and questions on home environment. Data from a video questionnaire designed to show various examples of wheeze and asthmatic attacks were also included in the CRF. Clinical data, including skin prick tests to 8 common allergens, total and specific IgE levels, and bronchial hyper-responsiveness following a methacholine challenge, were also collected from all participating family members. All data were entered into a SAS dataset (Statistical Analysis Software, Cary, NC) by IMTCI (International Medical Technical Consultants, Inc.) a Clinical Research Organization; either by double data entry or scanning followed by on-screen visual validation. An extensive automated review of the data was performed on a routine basis and a full audit at the conclusion of the data entry was completed to verify the accuracy of the dataset.

#### **EXAMPLE 2: Genome Scan**

In order to identify chromosomal regions linked to asthma, the inheritance pattern of alleles from genetic markers spanning the genome was assessed using the collected family resources. As described above, combining these results with the segregation of the asthma phenotype in these families allowed the identification of genetic markers that were tightly linked to asthma.

In turn, this provided an indication of the location of genes predisposing affected individuals to asthma. The genotyping strategy was twofold: 1) to conduct a genome wide scan using markers spaced at approximately 10 cM intervals; and 2) to target ten chromosomal regions for high density genetic mapping. The initial candidate regions for high-density mapping were chosen based on suggestions of linkage to these regions by other investigators.

Genotypes of PCR amplified simple sequence microsatellite genetic linkage markers were determined using ABI model 377 Automated Sequencers (Applied Biosystems, Inc.; Foster City, CA). Microsatellite markers were obtained from Research Genetics Inc. (Huntsville, AL) in the fluorescent dye-conjugated form (see Dubovsky et al., 1995, *Hum. Mol. Genet.* 4(3):449-452). The markers comprised a variation of a human linkage mapping panel as released from the Cooperative Human Linkage Center (CHLC), also known as the Weber lab screening set version 8. The variation of the Weber 8 screening set consisted of 535 markers with an average spacing of 6.8 cM (autosomes only) and 6.9 cM (all chromosomes). Eighty-nine percent of the markers consisted of either tri- or tetra-nucleotide microsatellites. There were no gaps present in chromosomal coverage greater than 17.5 cM.

Study subject genomic DNA (5 µl; 4.5 ng/µl) was amplified in a 10 µl PCR reaction using AmpliTaq Gold DNA polymerase (0.225 U); 1 X PCR buffer (80 mM (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>; 30 mM Tris-HCl (pH 8.8); 0.5% Tween-20); 200 µM each dATP, dCTP, dGTP and dTTP; 1.5-3.5 µM MgCl<sub>2</sub>; and 250 µM forward and reverse PCR primers. PCR reactions were set up in 192 well plates (Corning Costar, Acton, MA) using a Tecan Genesis 150 robotic workstation equipped with a refrigerated deck (Tecan Genesis, Durham, NC). PCR reactions were overlaid with 20 µl mineral oil, and thermocycled on an MJ Research Tetrad DNA Engine (MJ Research, Waltham, MA) equipped with four 192 well heads using the following conditions: 92°C for 3 min; 6 cycles of 92°C for 30 sec, 56°C for 1 min, 72°C for 45 sec; followed by 20 cycles of 92°C for 30 sec, 55°C for 1 min, 72°C for 45 sec; and a 6 min incubation at 72°C.

PCR products of 8-12 microsatellite markers were subsequently pooled

into two 96-well microtitre plates. This included 2.0 µl PCR product from TET and FAM labeled markers, 3.0 µl HEX labeled markers) using a Tecan Genesis 200 robotic workstation and brought to a final volume of 25 µl with H<sub>2</sub>O. Following this, 1.9 µl of pooled PCR product was transferred to a loading plate and combined with 3.0 µl loading buffer. Loading buffer included 2.5 µl formamide/blue dextran (9.0 mg/ml) and 0.5 µl GS-500 TAMRA labeled size standard (ABI, Foster City, CA). Samples were denatured in the loading plate for 4 min at 95°C, placed on ice for 2 min, and electrophoresed on a 5% denaturing polyacrylamide gel (BioWhittaker Molecular Applications, Rockland, ME) on the ABI 377XL). Samples (0.8 µl) were loaded onto the gel using an 8 channel Hamilton Syringe pipettor.

Each gel consisted of 62 study subjects and 2 control subjects (CEPH; Centre d'Etude du Polymorphisme Humain) parents ID #1331-01 and 1331-02, Coriell Cell Repository, Camden, NJ). Genotyping gels were scored in duplicate by investigators blind to patient identity and affection status using GENOTYPER analysis software V 1.1.12 (ABI; PE Applied Biosystems). Nuclear families were loaded onto the gel with the parents flanking the siblings to facilitate error detection. The final tables obtained from the GENOTYPER output for each gel analyzed were imported into a SYBASE Database (Dublin, CA).

Allele calling (binning) was performed using the SYBASE version of the ABAS software (Ghosh et al., 1997, *Genome Research* 7:165-178). Offsize bins were checked manually and incorrect calls were corrected or blanked. The binned alleles were then imported into the program MENDEL (Lange et al., 1988, *Genetic Epidemiology*, 5:471) for inheritance checking using the USERM13 subroutine (Boehnke et al., 1991, *Am. J. Hum. Genet.* 48:22-25). Non-inheritance was investigated by examining the genotyping traces and, once all discrepancies were resolved, the subroutine USERM13 (Boehnke et al., 1991, *Am. J. Hum. Genet.* 48:22-25) was used to estimate allele frequencies.

**EXAMPLE 3: Linkage Analysis**

Chromosomal regions harboring asthma susceptibility genes by linkage analysis of genotyping data and three separate phenotypes (asthma, bronchial hyper-responsiveness, and atopic status) were identified as follows.

- 5           1. Asthma Phenotype: For the initial linkage analysis, the phenotype and asthma affection status were defined by a patient who answered the following questions in the affirmative: i) have you ever had asthma; ii) do you have a current physician's diagnosis of asthma; and iii) are you currently taking asthma medications? Medications included inhaled or oral  
10 bronchodilators, cromolyn, theophylline, or steroids. Multipoint linkage analyses of allele sharing in affected individuals were performed using the MAPMAKER/SIBS analysis program (L. Kruglyak and E.S. Lander, 1995, *Am. J. Hum. Genet.* 57:439-454). The map location and distances between markers were obtained from the genetic maps published online by the  
15 Marshfield Medical Research Foundation, Marshfield, WI (hypertext transfer protocol on the world wide web at marshmed.org/genetics). Ambiguous ordering of markers in the Marshfield map was resolved using the program MULTIMAP (T.C. Matise et al., 1994, *Nature Genet.* 6:384-390).

- 20 Families with fewer than two genotyped asthmatic offspring were eliminated. Such families were due, for example, to non-paternity, sample mix-up, or DNA contamination. In the end, 460 pedigrees, containing 462 nuclear families each with at least one affected sib pair, were retained for analysis. Using the discrete phenotype of asthma (yes/no), a candidate region was identified on chromosome 20 with a LOD score of 2.94, based on the full set  
25 of 462 nuclear families. Figure 1 displays the multipoint LOD score against the map location of the markers along chromosome 20. A Maximum LOD Score (MLS) of 2.94 was obtained at location 7.9 cM, 0.3 cM proximal to marker D20S906. A second MLS of 2.94 was obtained at marker D20S482 at location 12.1 cM. An excess sharing by descent (Identity By Descent (IBD) = 2) of 0.31  
30 was observed at both maximum LOD scores. Table 2 lists the single and multipoint LOD scores at each marker. Analyses were done using a



conservative approach by weighting down multiple sibling pairs within a sibship. When affected sib pairs were utilized in the linkage analyses without weighting, the LOD score on chromosome 20 maximized at D20S482 with a value of 3.19. These data provided strong evidence for the presence of an

5 asthma susceptibility gene in this region of chromosome 20.

**TABLE 2**

Marker	Distance	Single-point	Multipoint
D20S502	0.5	0.7	2.4
D20S103	2.1	2.4	2.3
D20S117	2.8	1.2	2.0
GTC4ATG	6.3	2.4	2.5
GTC3CA	6.6	1.3	2.7
D20S906	7.6	2.9	2.9
D20S842	9.0	1.3	2.5
D20S181	9.5	1.8	2.6
D20S193	9.5	2.5	2.5
D20S889	11.2	1.6	2.6
D20S482	12.1	1.9	2.9
D20S849	14.0	0.8	2.0
D20S835	15.1	0.5	1.8
D20S448	18.8	1.4	1.4
D20S602	21.2	1.1	1.1
D20S851	24.7	1.0	0.8
D20S604	32.9	0.0	0.1
D20S470	39.3	0.0	0.1
D20S477	47.5	0.0	0.0
D20S478	54.1	0.0	0.0
D20S481	62.3	0.0	0.0
D20S480	79.9	0.0	0.0
D20S171	95.7	0.4	0.1

2. **Phenotypic Subgroups:** Nuclear families were ascertained by the presence of at least two affected siblings with a current physician's diagnosis of asthma, as well as the use of asthma medication. In the initial analysis (see above), the evidence was examined for linkage based on the dichotomous phenotype (asthma – yes/no). To further characterize the linkage signals, additional quantitative traits were measured in the clinical protocol. Since quantitative trait loci (QTL) analysis tools with correction for ascertainment

10 were not available, the following approach was taken to refine the linkage and association analyses:

15

i. Phenotypic subgroups that could be indicative of an underlying genotypic heterogeneity were identified. Asthma subgroups were defined according to 1) bronchial hyper-responsiveness (BHR) to methacholine challenge; or 2) to atopic status using quantitative measures like total serum IgE and specific IgE to common allergens.

ii. Non-parametric linkage analyses were performed on subgroups to test for the presence of a more homogeneous sub-sample. If genetic heterogeneity was present in the sample, the amount of allele sharing among phenotypically similar siblings was expected to increase in the appropriate subgroup in comparison to the full sample. A narrower region of significant increased allele sharing was also expected to result unless the overall LOD score decreased as a consequence of having a smaller sample size and of using an approximate partitioning of the data.

iii. Alternatively, allele sharing probabilities were parameterized as a function of the quantitative trait value of each child in a given sib pair, as advocated by N. Morton and implemented in his program BETA (N. Morton, 1996, *Proc. Natl. Acad. Sci. USA* **93**:3471-3476). This approach alleviated the need to dichotomize a quantitative trait. However, the program did not correct for the use of non-independent sib pairs in sibship of size 3 or larger. As such, it did not provide an accurate measure of the significance of a linkage finding, but was used to corroborate the localization of the linkage signal.

3. Results for BHR and IgE: PC<sub>20</sub>, the concentration of methacholine resulting in a 20% drop in FEV<sub>1</sub> (forced expiratory volume), was polychotomized in four groups. Analyses were performed on the subsets of asthmatic children with mild to severe BHR (PC<sub>20</sub> ≤ 4 mg/ml) or PC<sub>20</sub>(4), as well as on the broader subset with borderline to severe BHR (PC<sub>20</sub> ≤ 16 mg/ml) or PC<sub>20</sub>(16). As shown in the LOD plot in Figure 2, the MLS for the subset of 127 nuclear families with at least two PC<sub>20</sub>(4) affected sibs was 2.97 at 11.8 cM. This was 0.3 cM from D20S482, with an excess sharing by descent of 0.37. As shown in Figure 3, for the 218 nuclear families with at least two PC<sub>20</sub>(16),

the MLS was 3.93 at D20S482 with an excess sharing of 0.36. Both PC<sub>20</sub>(4) and PC<sub>20</sub>(16) strongly implicated the region of chromosome 20 under the second peak around marker D20S482. When considering the more extreme phenotype, PC<sub>20</sub>(4), a higher proportion of families was linked to the region.

5 However, the increase in LOD score for the PC<sub>20</sub>(16) phenotype indicated that families concordant for the milder BHR phenotype also contributed to the linkage signal and would provide a larger pool of linked families.

Total IgE was dichotomized using an age specific cutoff for elevated levels (one standard deviation above the mean). Similarly, a dichotomous

10 variable was created using specific IgE to common allergens. An individual was assigned a high specific IgE value if his/her level was positive (grass or tree) or elevated ( $> 0.35$  KU/L for cat, dog, mite A, mite B, alternaria, or ragweed) for at least one such measure. In linkage analyses, the subset of asthmatic children with high total IgE (274 families) was given a maximum LOD

15 score of 2.3 at 11.6 cM (Figure 4). The subset with high specific IgE (288 families) was given a LOD score of 1.87 at 12.1 cM (Figure 5). Similar to the BHR results, analyses based on IgE implicated the region under the second peak around marker D20S482. The substantially lower LOD scores using the subset of affected sibs concordant for atopy indicated the presence of groups

20 with fewer linked families. Thus, atopy in asthmatic individuals was not the primary phenotype associated with the linkage signal on chromosome 20.

The BETA program (Morton, 1996) was used on two scales for PC<sub>20</sub>. Individuals that did not drop 20% by the last dose administered (16 mg/ml) were assigned an arbitrary value of 32 mg/ml. First, a (0,1)-severity scale was

25 constructed by applying a linear transformation to PC<sub>20</sub> where 0 mg/ml received a score of 1 and 32 mg/ml received a score of 0. For this scale, individuals that did not drop 20% in their FEV<sub>1</sub> did not contribute to the LOD score. A maximum LOD score of 3.43 was achieved at 12.1 cM with marker D20S482. Second, a linear transformation of PC<sub>20</sub> was used where 0 mg/ml

30 received a score of 1 and 32 mg/ml a score of -1. In other words, in addition to the high concordant pairs, discordant pairs and concordant pairs that did not

drop would also contribute to the LOD score. In contrast, individuals with PC<sub>20</sub> close to 16 mg/ml would have little impact on the LOD score. A maximum LOD score of 2.08 was again achieved at 12.1 cM.

Accordingly, a consistent pattern of evidence by linkage analysis pointed to the existence of an asthma susceptibility locus in the vicinity of marker D20S482. This was supported by the initial analysis of the asthma (yes/no) phenotype and by analyses of BHR in asthmatic individuals. Localization in the region of marker D20S482 was obtained using both BHR and IgE phenotypes.

#### **EXAMPLE 4: Physical Mapping**

The linkage results for chromosome 20 described above were used to delineate a candidate region for a disorder-associated gene located on chromosome 20. Gene discovery efforts were initiated in a 25 cM interval from the 20p telomere (marker D20S502) to marker D20S851. This represented a >98% confidence interval. All genes known to map to this interval were considered as candidates. Intensive physical mapping (BAC contig construction) focused on a 90% confidence interval between markers D20S103 and D20S916, a 15 cM interval. The discovery of novel genes using direct cDNA selection focused on a 95% confidence interval between markers D20S502 (20p telomere) and D20S916, a 17 cM region.

The following section describes the generation of cloned coverage of the disorder gene region on chromosome 20, i.e., the construction of a BAC contig spanning the region. There were two primary reasons for using this approach: 1) to provide genomic clones for DNA sequencing (analysis of this sequence would provide information about the gene content of the region); and 2) to provide reagents for direct cDNA selection (this would provide additional information about novel genes mapping to the interval). The physical map consisted of an ordered set of molecular landmarks, and a set of bacterial artificial chromosome clones (BACs; U.-J. Kim et al., 1996, *Genomics* **34**:213-218; H. Shizuya et al., 1992, *Proc. Natl. Acad. Sci. USA* **89**:8794-8797) that contained the disorder gene region from human chromosome 20p13-p12.

Figure 6 depicts the BAC/STS (sequence tagged site) content contig

map of human chromosome 20p13-p12. Markers used to screen the RPCI-11 BAC library (P. deJong, Roswell Park Cancer Institute (RPCI)) are shown in the top row. Markers that were present in the Genome Database website (GDB; 5  
hypertext transfer protocol on the world wide web at gdb.org; GDB, Toronto, Canada) are represented by GDB nomenclature. The BAC clones are shown below the markers as horizontal lines. BAC RPCI-11\_1098L22 is labeled, and the location of Gene 216, described herein, is indicated at the top of the figure.

1. Map Integration. Various publicly available mapping resources were utilized to identify existing STS markers (Olson et al., 1989, *Science*, 10  
**245**:1434-1435) in the 20p13-p12 region. Online resources included the GDB website, the Genethon website (hypertext transfer protocol on the world wide web at the site genethon.fr/genethon\_en.html), the Marshfield Center for Medical Genetics website (hypertext transfer protocol on the world wide web at marshmed.org/genetics), the Whitehead Institute Genome Center website 15  
(hypertext transfer protocol on the world wide web at genome.win.mit.edu; Whitehead Institute, Cambridge, MA), GeneMap98, dbSTS and dbEST (NCBI), the Sanger Center website (hypertext transfer protocol on the world wide web at sanger.ac.uk; Sanger Center, Hinxton, England), and the Stanford Human Genome Center website (hypertext transfer protocol on the world wide web at shgc.stanford.edu; Stanford HGC, Stanford, CA). Maps were integrated 20  
manually to identify markers mapping to the disorder region. A list of the markers is provided in Table 3.

2. Marker Development: Sequences for existing STSs were obtained from the GDB website, RHDB website (Radiation Hybrid Database, 25  
hypertext transfer protocol on the world wide web at ebi.ac.uk/RHdb; RHDB, Hinxton, England), or NCBI, and were used to pick primer pairs (overgos; see Table 3) for BAC library screening. Novel markers were developed either from publicly available genomic sequences, proprietary cDNA sequences, or from sequences derived from BAC insert ends (described below). Primers were 30  
chosen using a script that automatically performed vector and repetitive sequence masking using CROSSMATCH (P. Green, University of

Washington). Subsequent primer selection was performed using a customized online Filemaker Pro database (hypertext transfer protocol on the world wide web at filemaker.com; Filemaker Pro, Santa Clara, CA). Primers for use in PCR-based clone confirmation or radiation hybrid mapping (described below) were chosen using the program Primer3 (S. Rozen, H. Skaletsky, 2000, *Mol. Biol.* **132**:365-86; hypertext transfer protocol on the world wide web at genome.wi.mit.edu/genome\_software/other /primer3.html).

TABLE 3

Overgo	Locus	DNA Type	Gene	Forward Primer	SEQ ID NO	Reverse Primer	SEQ ID
stSG24277		Genomic		aactctgaaatgagaagcgtg	34	aaccaccacggalttaacgcttc	45
stSG408		EST		aatatcatgcaacatgaocceac	35	ataaccagatggcgtgggtca	46
A005005		EST	Attractin (ATTN)	tggagtaagiatatgiaaactat	36	atccccgcaatgaaaatagttta	47
B849D17AL		BACend		ggagcttatctctggattatcta	37	gttgagagcccactitagataat	48
SN2		EST	Sialoadhesin (SN)	agagccacacatccaigtccig	38	gcatggggggaagccaggacat	49
AFMb026xh5	D20S867	MSAT		aagccactctgtgaattgccat	39	gccactaggaggccaatggcaat	50
SN1		EST	Sialoadhesin (SN)	gagtagtgtagtaccagaatgg	40	cgacggcaatcacggccatctgg	51
stSH22126		EST		gtctggcaatggagcattgaaaa	41	tcacggctcatctatfftcattg	52
W14876	D20S752	Genomic		attagagcacatgaaggaaagg	42	tgacatcaactctctcttctct	53
stSG30448		EST		acactgctttggggacaggct	43	agttgcagagacctaagccgttc	54
W118677		EST		cacgaogccacagagccagctc	44	tcctggagaggagcaggtctggc	55

3.     Radiation Hybrid (RH) Mapping: Radiation hybrid mapping was performed against the Genebridge4 panel (Gyapay et al., 1996, *Hum. Mol. Genet.* 5:339-46) purchased from Research Genetics, in order to refine the chromosomal localization of genetic markers used in genotyping. Mapping was also performed to identify, confirm, and refine localizations of markers from proprietary sequences. Standard PCR procedures were used for typing the RH panel with markers of interest. Briefly, 10 µl PCR reactions contained 25 ng DNA of each of the 93 Genebridge4 RH samples. PCR products were electrophoresed on 2% agarose gels (Sigma, St. Louis, MO) containing 0.5 µg/ml ethidium bromide in 1 X TBE at 150 volts for 45 min.

For electrophoresis, Model A3-1 systems were used (Owl Scientific Products, Portsmouth, NH). Typically, gels contained 10 tiers of lanes with 50 wells/tier. Molecular weight markers (100 bp ladder, GibcoBRL, Rockville, MD) were loaded at both ends of the gel. Images of the gels were captured with a Kodak DC40 CCD camera and processed with Kodak 1D software (Kodak, Rochester, NY). The gel data were exported as tab delimited text files; names of the files included information about the panel screened, the gel image files and the marker screened. These data were automatically imported using a customized Perl script into Filemaker databases for data storage and analysis.

The data were then automatically formatted and submitted to an internal server for linkage analysis to create a radiation hybrid map using RHMAPPER (L. Stein et al., 1995; available from Whitehead Institute/MIT Center for Genome Research, at hypertext transfer protocol on the world wide web at [genome.wi.mit.edu/ftp/pub/software/rhmapper](http://genome.wi.mit.edu/ftp/pub/software/rhmapper); Whitehead Institute, Cambridge, MA; and via anonymous ftp to [ftp.genome.wi.mit.edu](ftp://ftp.genome.wi.mit.edu), in the directory/pub/software/rhmapper).

4.     BAC Library Screening: The protocol used for BAC library screening was based on the "overgo" method, originally developed by John McPherson at Washington University in St. Louis (W-W. Cai et al., 1998, *Genomics* 54:387-397). This method involved filling in the overhangs generated after annealing two primers. Each primer was 22 nucleotides in



length, and overlapped by 8 nucleotides. The resulting labeled 36 bp product was used in hybridization-based screening of high density grids derived from the RPCI-11 BAC library (deJong, *supra*). Typically, 15 probes were pooled together to hybridize 12 filters (13.5 genome equivalents).

5        Stock solutions (2  $\mu$ M) of combined complementary oligos (Table 3) were heated at 80°C for 5 min, placed at 37°C for 10 min, and then stored on ice. Labeling reactions included the following: 1.0  $\mu$ l H<sub>2</sub>O; 5  $\mu$ l mixed oligos (2  $\mu$ M each); 0.5  $\mu$ l BSA (2 mg/ml); 2  $\mu$ l OLB (Overgo Labeling Buffer) Solution (see below); 0.5  $\mu$ l <sup>32</sup>P-dATP (3000 Ci/mmol); 0.5  $\mu$ l <sup>32</sup>P-dCTP (3000 Ci/mmol);  
10       and 0.5  $\mu$ l Klenow fragment (5 U/ $\mu$ l). The reaction was incubated at room temperature for 1 hr, and unincorporated nucleotides were removed using Sephadex G50 spin columns (Pharmacia, Piscataway, NJ). Solution O: 1.25 M Tris-HCL, pH 8, 125 M MgCl<sub>2</sub>; Solution A: 1 ml Solution O, 18  $\mu$ l 2-mercaptoethanol, 5 $\mu$ l 0.1M dTTP, 5 $\mu$ l 0.1 M dGTP; Solution B: 2 M HEPES-  
15       NaOH, pH 6.6; Solution C: 3 mM Tris-HCl, pH 7.4, 0.2 mM EDTA; Solution OLB: Solutions A, B, and C were combined to a final ratio of 1:2.5:1.5, and aliquots were stored at -20°C.

High-density BAC library membranes were pre-wetted in 2 X SSC at 58°C. Filters were then drained slightly and placed in hybridization solution  
20       (1% BSA; 1 mM EDTA, pH 8.0; 7% SDS; and 0.5 M sodium phosphate), pre-warmed to 58°C, and incubated at 58°C for 2-4 hr. Typically, 6 filters were hybridized in each container. Ten milliliters of pre-hybridization solution was removed, combined with the denatured overgo probes, and added back to the filters. Hybridization was performed overnight at 58°C. The hybridization  
25       solution was removed and filters were washed once in 2 X SSC, 0.1% SDS, followed by a 30 min wash in the same solution at 58°C. Filters were then washed in: 1) 1.5 X SSC and 0.1% SDS at 58°C for 30 min; 2) 0.5 X SSC and 0.1% SDS at 58°C for 30 min; and finally in 3) 0.1 X SSC and 0.1% SDS at 58°C for 30 min. Filters were then wrapped in Saran Wrap® and exposed to  
30       film overnight. To remove bound probe, filters were treated in 0.1 X SSC and 0.1% SDS pre-warmed to 95°C and cooled room temperature. Clone

addresses were determined as described by instructions supplied by RPCI.

To recover clonal BAC cultures from the library, a sample from the appropriate library well was plated by streaking onto LB agar (T. Maniatis et al., 1982, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY) containing 12.5 µg/ml chloramphenicol (Sigma). Plates were incubated overnight at 37°C. A single colony and a portion of the initial streak quadrant were inoculated into 400 µl LB plus chloramphenicol in wells of a 96 well plate. Cultures were grown overnight at 37°C. For storage, 100 µl of 80% glycerol was added and the plates placed at -80°C.

To determine the marker content of clones, aliquots of the 96 well plate cultures were transferred to the surface of nylon filters (GeneScreen Plus, NEN) placed on LB/chloramphenicol Petri plates. Colonies were grown overnight at 37°C and colony lysis was performed by placing filters on pools of: 1) 10% SDS for 3 min; 2) 0.5 N NaOH and 1.5 M NaCl for 5 min; and 3) 0.5 M Tris-HCl, pH 7.5, and 1 M NaCl for 5 min. Filters were then air-dried and washed free of debris in 2 X SSC for 1 hr. The filters were air-dried for at least 1 hr and DNA was crosslinked linked to the membrane using standard conditions. Probe hybridization and filter washing were performed as described above for the primary library screening. Confirmed clones were stored in LB containing 15% glycerol.

In certain cases, polymerase chain reaction (PCR) was used to confirm the marker content of clones. PCR conditions for each primer pair were initially optimized with respect to MgCl<sub>2</sub> concentration. The standard buffer was 10 mM Tris-HCl (pH 8.3), 50 mM KCl, MgCl<sub>2</sub>, 0.2 mM each dNTP, 0.2 µM each primer, 2.7 ng/µl human DNA, 0.25 units of AmpliTaq (Perkin Elmer) and MgCl<sub>2</sub> concentrations of 1.0 mM, 1.5 mM, 2.0 mM or 2.4 mM. Cycling conditions included an initial denaturation at 94°C for 2 min; followed by 40 cycles at 94°C for 15 sec, 55°C for 25 sec, and 72°C for 25 sec; followed by a final extension at 72°C for 3 min. Depending on the results from the initial round of optimization the conditions were further optimized. Variables included increasing the annealing temperature to 58°C or 60°C, increasing the cycle

number to 42 and the annealing and extension times to 30 sec, and using AmpliTaqGold (Perkin Elmer).

5        5.    BAC DNA Preparation: Several different types of DNA preparation methods were used for isolation of BAC DNA. The manual alkaline lysis miniprep protocol listed below (Maniatis et al., 1982) was successfully used for most applications, i.e., restriction mapping, CHEF gel analysis and FISH mapping, but was not reproducibly successful in endsequencing. The Autogen protocol was used specifically for BAC DNA preparation for endsequencing.

10        For manual alkaline lysis BAC minipreps, bacteria were grown in 15 ml terrific broth (TB) containing 12.5 µg/ml chloramphenicol. Cultures were placed in a 50 ml conical tube at 37°C for 20 hr with shaking at 300 rpm. The cultures were centrifuged in a Sorvall RT 6000 D (Sorvall, Newton, CT) at 3000 rpm (1800 x g) at 4°C for 15 min. The supernatant was then aspirated as completely as possible. In some cases cell pellets were frozen at -20°C at this step for up to 2 weeks. The pellet was then vortexed to homogenize the cells and minimize clumping. Following this, 250 µl of P1 solution (50 mM glucose, 15 mM Tris-HCl, pH 8, 10 mM EDTA, and 100 µg/ml RNase A) was added, and the mixture was pipetted up and down to mix. The mixture was then transferred to a 2 ml Eppendorf tube. Subsequently, 350 µl of P2 solution (0.2 N NaOH, 1% SDS) was added, mixed gently, and the mixture was incubated for 5 min at room temperature. Then, 350 µl of P3 solution (3 M KOAc, pH 5.5) was added and mixed gently until a white precipitate formed. The solution was incubated on ice for 5 min and then centrifuged at 4°C in a microfuge for 10 min.

20        The supernatant was transferred carefully (avoiding the white precipitate) to a fresh 2 ml Eppendorf tube. Then, 0.9 ml of isopropanol was added, and the solution was mixed and left on ice for 5 min. The samples were centrifuged for 10 min, and the supernatant removed carefully. Pellets were washed in 70% ethanol and air-dried for 5 min. Pellets were resuspended in 200 µl of TE8 (10 mM Tris-HCl, pH 8.0, 1.0 mM EDTA, pH

8.0), and RNase (Boehringer Mannheim, Indianapolis, IN; hypertext transfer protocol at [biochem.boehringer-mannheim.com](http://biochem.boehringer-mannheim.com)) added to 100 µg/ml. Samples were incubated at 37°C for 30 min. DNA was precipitated by addition of NH<sub>4</sub>OAc to 0.5 M and 2 volumes of ethanol. Samples were centrifuged for 10 min, and the pellets were washed with 70% ethanol. The pellets were air-dried and dissolved in 50 µl TE8. Typical yields for this DNA prep were 3-5 µg per 15 ml bacterial culture. Ten to fifteen microliters of DNA was used for *EcoRI* restriction analysis. Five microliters was used for *NotI* digestion and clone insert sizing by CHEF gel electrophoresis.

Autogen 740 BAC DNA preparations for endsequencing were made by dispensing 3 ml of LB media containing 12.5 µg/ml of chloramphenicol into autoclaved Autogen tubes. A single tube was used for each clone. For inoculation, glycerol stocks were removed from -70°C storage and placed on dry ice. A small portion of the glycerol stock was removed from the original tube with a sterile toothpick and transferred into the Autogen tube. The toothpick was left in the Autogen tube for at least two min before discarding. After inoculation the tubes were covered with tape to ensure that the seal was tight. When all samples were inoculated, the tubes were transferred into an Autogen rack holder and placed into a rotary shaker. Cultures were incubated at 37°C for 16-17 hr at 250 rpm. Following this, standard conditions for BAC DNA preparation, as defined by the manufacturer, were used to program the Autogen. However, samples were not dissolved in TE8 as part of the program. Instead, DNA pellets were left dry.

When the program was completed, the tubes were removed from the output tray and 30 µl of sterile distilled and deionized H<sub>2</sub>O was added directly to the bottom of the tube. The tubes were then gently shaken for 2-5 sec and then covered with parafilm and incubated at room temperature for 1-3 hr. DNA samples were then transferred to an Eppendorf tube and used either directly for sequencing or stored at 4°C for later use.

6. BAC Clone Characterization: DNA samples prepared either by manual alkaline lysis or the Autogen protocol were digested with *EcoRI* for

analysis of restriction fragment sizes. These data were used to compare the extent of overlap among clones. Typically 1-2 µg were used for each reaction.

Reaction mixtures included: 1 X Buffer 2 (NEB, Beverly, MA); 0.1 mg/ml BSA (NEB); 50 µg/ml RNase A (Boehringer Mannheim); and 20 units of *EcoRI* (NEB) in a final volume of 25 µl. Digestions were incubated at 37°C for 4-6 hr.

BAC DNA was also digested with *NotI* for estimation of insert size by CHEF gel analysis (see below). Reaction conditions were identical to those for *EcoRI*, except that 20 units of *NotI* were used. Six microliters of 6 X Ficoll loading buffer containing bromophenol blue and xylene cyanol was added prior to electrophoresis.

*EcoRI* digests were analyzed on 0.6% agarose (Seakem, FMC Bioproducts, Rockland, ME) in 1X TBE containing 0.5 µg/ml ethidium bromide. Gels (20 cm x 25 cm) were electrophoresed in a Model A4 electrophoresis unit (Owl Scientific) at 50 volts for 20-24 hr. Molecular weight size markers included undigested lambda DNA, *HindIII* digested lambda DNA, and *HaeIII* digested .X174 DNA. Molecular weight markers were heated at 65°C for 2 min prior to loading the gel. Images were captured with a Kodak DC40 CCD camera and analyzed with Kodak 1D software.

*NotI* digests were analyzed on a CHEF DRII (Bio-Rad, Hercules, CA) electrophoresis unit according to the manufacturer's recommendations. Briefly, 1% agarose gels (Bio-Rad pulsed field grade) were prepared in 0.5 X TBE. Gels were equilibrated for 30 min in the electrophoresis unit at 14°C, and electrophoresed at 6 volts/cm for 14 hr with circulation. Switching times were ramped from 10 sec to 20 sec. Gels were stained after electrophoresis in 0.5 µg/ml ethidium bromide. Molecular weight markers included undigested lambda DNA, *HindIII* digested lambda DNA, lambda ladder PFG ladder, and low range PFG marker (all from NEB).

7. BAC Endsequencing: The sequence of BAC insert ends utilized DNA prepared by either of the two methods described above. The ends of BAC clones were sequenced for the purpose of filling gaps in the physical map and for gene discovery information. The following vector primers specific to the

BAC vector pBACe3.6 were used to generate endsequence from BAC clones: pBAC 5'-2 (TGT AGG ACT ATA TTG CTC; SEQ ID NO:56) and pBAC 3'-1 (CGA CAT TTA GGT GAC ACT; SEQ ID NO:57).

5 The ABI dye-terminator sequencing protocol was used to set up sequencing reactions for 96 clones. The BigDye (ABI; PE Applied Biosystems) Terminator Ready Reaction Mix with AmpliTaq<sup>®</sup> FS, Part number 4303151, was used for sequencing with fluorescently labeled dideoxy nucleotides. A master sequencing mix was prepared for each primer reaction set including: 1600 µl of BigDye terminator mix (ABI; PE Applied Biosystems); 800 µl of 5 X CSA  
10 buffer (ABI; PE Applied Biosystems); and 800 µl of primer (either pBAC 5'-2 or pBAC 3'-1 at 3.2 µM). The sequencing cocktail was vortexed to ensure it was well-mixed and 32 µl was aliquotted into each PCR tube. Eight microliters of the Autogen DNA for each clone was transferred from the DNA source plate to a corresponding well of the PCR plate. The PCR plates were sealed tightly  
15 and centrifuged briefly to collect all the reagents. Cycling conditions were as follows: 1) 95°C for 5 min; 2) 95°C for 30 sec; 3) 50°C for 20 sec; 4) 65°C for 4 min; 5) steps 2 through 4 were repeated 74 times; and 6) samples were stored at 4°C.

At the end of the sequencing reaction, the plates were removed from the  
20 thermocycler and centrifuged briefly. Centri•Sep 96-well plates (Princeton Separations Inc., Adelphia, NJ) were then used according to manufacturer's recommendations to remove unincorporated nucleotides, salts, and excess primers. Each sample was resuspended in 1.5 µl of loading dye, and 1.3 µl of the mixture was loaded on ABI 377 Fluorescent Sequencers. The resulting  
25 endsequences were then used to develop markers to rescreen the BAC library for filling gaps and were also analyzed by BLASTN2 searching for EST or gene content in GenBank.

#### **EXAMPLE 5: Subcloning and Sequencing of BAC RPCI-11 1098L22**

The physical map of the chromosome 20 region provided the location  
30 of the BAC RPCI-11\_1098L22 clone that contains Gene 216 (see Figure 6). The BAC RPCI-11\_1098L22 clone was deposited as clone RP11-1098L22

with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209 USA, under ATCC Designation No. PTA-3171, on March 14, 2001 according to the terms of the Budapest Treaty. DNA sequencing of BAC RPCI-11-1098L22 from the region was completed. BAC  
5 RPCI-11-1098L22 DNA, (the "BAC DNA") was isolated according to one of two protocols: either a QIAGEN purification (QIAGEN, Inc., Valencia, CA, per manufacturer's instructions) or a manual purification using a method which was a modification of the standard alkaline lysis/cesium chloride preparation of plasmid DNA (see e.g., F.M. Ausubel et al., 1997, *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY). Briefly, for the manual  
10 protocol, cells were pelleted, resuspended in GTE (50 mM glucose, 25 mM Tris-Cl (pH 8), 10 mM EDTA) and lysozyme (50 mg/ml solution), followed by addition of NaOH/SDS (1% SDS and 0.2 N NaOH) and then an ice-cold solution of 3 M KOAc (pH 4.5-4.8). RnaseA was added to the filtered  
15 supernatant, followed by treatment with Proteinase K and 20% SDS. The DNA was then precipitated with isopropanol, dried, and resuspended in TE (10 mM Tris, 1 mM EDTA - pH 8.0). The BAC DNA was further purified by cesium chloride density gradient centrifugation (Ausubel et al., 1997).

Following isolation, the BAC DNA was hydrodynamically sheared using  
20 HPLC (Hengen et al., 1997, *Trends in Biochem. Sci.*, **22**:273-274) to an insert size of 2000-3000 bp. After shearing, the DNA was concentrated and separated on a standard 1% agarose gel. A single fraction, corresponding to the approximate size, was excised from the gel and purified by electroelution (Sambrook et al., 1989).

25 The overhangs of the purified DNA fragments were filled-in using T4 DNA polymerase. The blunt-ended DNA was ligated to unique *Bst*XI-linker adapters in 100-1000 fold molar excess. The sequence of the adapters was: 5' GTCTTCACACGGGG (SEQ ID NO:58) and 5' GTGGTGAAGAC (SEQ ID NO:59). The linkers were complimentary to the *Bst*XI-cut pMPX vectors, but  
30 the overhangs were not self-complimentary. Therefore, it was expected that the linkers would not concatemerize, and that the cut-vector would not re-ligate

on itself. The linker-adapted inserts were separated from unincorporated linkers on a 1% agarose gel and purified using GeneClean (BIO 101, Inc., Vista, CA). The linker-adapted insert was then ligated to a modified pBlueScript vector to construct a "shotgun" subclone library. The vector  
5 contained an out-of-frame lacZ gene at the cloning site, which became in-frame in the event that an adapter-dimer was cloned. Such adapter-dimer clones gave rise to blue colonies, which were avoided.

All subsequent steps were based on sequencing by ABI377 automated DNA sequencing methods. Major modifications to the protocols are highlighted  
10 below. Briefly, the library was transformed into DH5 $\alpha$  -competent cells (GibcoBRL, DH5 $\alpha$  -transformation protocol). Transformants were plated onto LB plates containing ampicillin (50  $\mu$ g/ml) and IPTG/X-gal. The plates were incubated overnight at 37°C. White colonies were identified and then used to plate individual clones for sequencing. The cultures were grown overnight at  
15 37°C. DNA was purified using a silica bead DNA preparation method (Ng et al., 1996, *Nucl. Acids Res.*, **24**:5045-5047). In this manner, 25  $\mu$ g of DNA was obtained per clone.

These purified DNA samples were sequenced using ABI dye-terminator chemistry. The ABI dye terminator sequence reads were run on ABI377  
20 machines and the data were directly transferred to UNIX machines following lane tracking of the gels. All reads were assembled using PHRAP (P. Green, *Abstracts of DOE Human Genome Program Contractor-Grantee Workshop V*, Jan. 1996, p.157) with default parameters and quality scores. The assembly was done at 8-fold coverage and yielded 1 contig, BAC RPCI-11-1098L22.  
25 SEQ ID NO:5 (Figure 7) comprises a portion of the BAC that includes the genomic sequence of Gene 216.

#### **EXAMPLE 6: Gene Identification**

Any gene or EST mapping to the interval based on public map data or proprietary map data was considered a candidate respiratory disease gene.  
30 Public map data were derived from several online sources: the Genome Database website (GDB), the Whitehead Institute Genome Center website,



GeneMap98, UniGene, OMIM, dbSTS and dbEST (NCBI) the Sanger Center website, and the Stanford Human Genome Center website. Proprietary data was obtained from sequencing genomic DNA (cloned into BACs) or cDNAs (identified by direct selection, screening of cDNA libraries, or full length  
5 sequencing of the IMAGE Consortium cDNA clones available online (hypertext transfer protocol on the world wide web at [bio.11nl.gov/bbrp/image.html](http://bio.11nl.gov/bbrp/image.html)).

1. Gene Identification from clustered DNA fragments. DNA sequences corresponding to gene fragments in public databases (GenBank and human dbEST) and proprietary cDNA sequences (IMAGE consortium and  
10 direct selected cDNAs) were masked for repetitive sequences and clustered using the PANGAEA Systems (Oakland, CA) EST clustering tool. The clustered sequences were then subjected to computational analysis to identify regions bearing similarity to known genes. This protocol included the following steps:

a. The clustered sequences were compared to the publicly available  
15 UniGene database (NCBI) using the BLASTN2 algorithm (Altschul et al., 1997). The parameters for this search were:  $E = 0.05$ ,  $v = 50$ ,  $B = 50$ , where  $E$  was the expected probability score cutoff,  $V$  was the number of database entries returned in the reporting of the results, and  $B$  was the number of sequence alignments returned in the reporting of the results (Altschul et al., 1990).

20 b. The clustered sequences were compared to the GenBank database (NCBI) using BLASTN2 (Altschul et al., 1997). The parameters for this search were  $E=0.05$ ,  $V=50$ ,  $B= 50$ , where  $E$ ,  $V$ , and  $B$  were defined as above.

c. The clustered sequences were translated into protein sequences for all six reading frames, and the protein sequences were compared to a non-redundant protein database compiled from GenPept Swissprot PIR (NCBI).  
25 The parameters for this search were  $E = 0.05$ ,  $V = 50$ ,  $B = 50$ , where  $E$ ,  $V$ , and  $B$  were defined as above.

d. The clustered sequences were compared to BAC sequences (see below) using BLASTN2 (Altschul et al., 1997). The parameters for this search  
30 were  $E=0.05$ ,  $V=50$ ,  $B=50$ , where  $E$ ,  $V$ , and  $B$  were defined as above.

2. Gene Identification from BAC Genomic Sequence: Following

assembly of the BAC sequences into contigs, the contigs were subjected to computational analyses to identify coding regions and regions bearing DNA sequence similarity to known genes. This protocol included the following steps:

- a. Contigs were degapped. The sequence contigs often contained  
5 symbols (denoted by a period symbol) that represented locations where the individual ABI sequence reads had insertions or deletions. Prior to automated computational analysis of the contigs, the periods were removed. The original data were maintained for future reference.
- b. BAC vector sequences were "masked" within the sequence by using  
10 the program CROSSMATCH (P. Green, University of Washington). The shotgun library construction detailed above left some BAC vector in the shotgun libraries. Accordingly, the CROSSMATCH program was used to compare the sequence of the BAC contigs to the BAC vector and to mask any vector sequence prior to subsequent steps. Masked sequences were marked  
15 by "X" in the sequence files, and remained inert during subsequent analyses.
- c. *E. coli* sequences contaminating the BAC sequences were masked by comparing the BAC contigs to the entire *E. coli* DNA sequence.
- d. Repetitive elements known to be common in the human genome were masked using CROSSMATCH (P. Green, University of Washington). In  
20 this implementation of CROSSMATCH, the BAC sequence was compared to a database of human repetitive elements (J. Jerka, Genetic Information Research Institute, Palo Alto, CA). The masked repeats were marked by "X" and remained inert during subsequent analyses.
- e. The location of exons within the sequence was predicted using the  
25 MZEF computer program (Zhang, 1997, *Proc. Natl. Acad. Sci.*, **94**:565-568) and GenScan gene prediction program (Burge and Karlin, *J. Mol. Biol.*, **268**:78-94).
- f. The sequence was compared to the publicly available UniGene database (NCBI) using the BLASTN2 algorithm (Altschul et al., 1997). The  
30 parameters for this search were:  $E = 0.05$ ,  $v = 50$ ,  $B = 50$ , where  $E$  was the expected probability score cutoff,  $V$  was the number of database entries

returned in the reporting of the results, and B was the number of sequence alignments returned in the reporting of the results (Altschul et al., 1990).

g. The sequence was translated into protein sequences for all six reading frames, and the protein sequences were compared to a non-redundant protein database compiled from GenPept, Swissprot, and PIR (NCBI). The parameters for this search were  $E = 0.05$ ,  $V = 50$ ,  $B = 50$ , where E, V, and B were defined as above.

h. The BAC DNA sequence was compared to a database of clustered sequences using the BLASTN2 algorithm (Altschul et al., 1997). The parameters for this search were  $E = 0.05$ ,  $V = 50$ ,  $B = 50$ , where E, V, and B were defined as above. The database of clustered sequences was prepared utilizing a proprietary clustering technology (PANGAEA Systems, Inc.). The database included cDNA clones derived from direct selection experiments (described below), human dbEST sequences mapping to the 20p13-p12 region, proprietary cDNAs, GenBank genes, and IMAGE consortium cDNA clones.

i. Using the BLASTN2 algorithm (Altschul et al., 1997), the BAC sequence was compared to the sequences derived from the ends of BACs from the region on chromosomes 20. The parameters for this search were  $E = 0.05$ ,  $V = 50$ ,  $B = 50$ , where E, V, and B were defined as above.

j. The BAC sequence was compared to the GenBank database (NCBI) using the BLASTN2 algorithm (Altschul et al., 1997). The parameters for this search were  $E = 0.05$ ,  $V = 50$ ,  $B = 50$ , where E, V, and B were defined as above.

k. The BAC sequence was compared to the STS division of GenBank database (NCBI) using the BLASTN2 algorithm (Altschul et al., 1997). The parameters for this search were  $E=0.05$ ,  $V=50$ ,  $B= 50$ , where E, V, and B were defined as above.

l. The BAC sequence was compared to the Expressed Sequence Tag (EST) GenBank database (NCBI) using the BLASTN2 algorithm (Altschul et al., 1997). The parameters for this search were  $E = 0.05$ ,  $V = 50$ ,  $B = 50$ , where

E, V, and B were defined as above.

3. Mapping Analysis

Through mapping analysis, BAC RPCI-11\_1098L22 (ATCC Designation No. PTA-3171) was identified as containing Gene 216. This BAC sequence  
5 (SEQ ID NO:5; Figure 7) included the genomic sequence of Gene 216 (SEQ ID NO:6; Figure 29), which corresponded to the cDNA sequence of Gene 216 (SEQ ID NO:1; Figure 24).

**EXAMPLE 7: Gene 216 cDNA Cloning and Expression Analysis**

1. Construction and screening of cDNA libraries: Directionally  
10 cloned cDNA libraries from normal lung and bronchial epithelium were constructed using standard methods (Soares et al., 1994, *Automated DNA Sequencing and Analysis*, Adams et al. (eds), Academic Press, NY, pp. 110-114). Total and cytoplasmic RNAs were extracted from tissue or cells by homogenizing samples in the presence of guanidinium thiocyanate-phenol-  
15 chloroform extraction buffer (e.g. Chomczynski and Sacchi, 1987, *Anal. Biochem.*, **162**:156-159) using a polytron homogenizer (Brinkman Instruments, Westbury, NY). Poly(A)+ RNA was isolated from total/cytoplasmic RNA using dynabeads-dT according to the manufacturer's recommendations (DynaL, Inc., Lake Success, NY). The double stranded cDNA was then ligated into the  
20 plasmid vector pBluescript II KS+ (Stratagene, La Jolla, CA), and the ligation mixture was transformed into *E. coli* host DH10B or DH12S by electroporation (Soares et al., 1994). Transformants were grown at 37°C overnight. DNA was recovered from the *E. coli* colonies after scraping the plates by processing as directed for the Mega-prep kit (QIAGEN). The quality of the cDNA libraries was  
25 estimated by 1) counting a portion of the total number of primary transformants; 2) determining the average insert size; and 3) calculating the percentage of plasmids with no cDNA insert. Additional cDNA libraries (human total brain, heart, kidney, leukocyte, and fetal brain) were purchased from Life Technologies (Bethesda, MD).  
30 cDNA libraries were used for isolating cDNA clones mapped within the disorder critical region. The libraries were oligo (dT) and random hexamer-

primed. Four 10 x 10 arrays of each of the cDNA libraries were prepared as follows. The cDNA libraries were titered to  $2.5 \times 10^6$  cfu using primary transformants. The appropriate volume of frozen stock was used to inoculate 2 L of LB with ampicillin (100 µg/µl final concentration). Four hundred aliquots  
5 containing 4 ml of the inoculated liquid culture were generated. Each tube contained about 5000 cfu (colony forming units). The tubes were incubated at 30°C overnight with shaking until an OD of 0.7-0.9 was obtained. Frozen stocks were prepared for each of the cultures by aliquotting 300 µl of culture and 100 µl of 80% glycerol. Stocks were frozen in a dry ice/ethanol bath and  
10 stored at -70°C. DNA was isolated from the remaining culture using the QIAGEN spin mini-prep kit according to the manufacturer's instructions. The DNA from the 400 cultures was pooled to make 40 column pools and 40 row pools. For this, 4 boxes were prepared; each box contained 10 rows and 10 columns of samples to yield a total of 40 rows and 40 columns of samples.  
15 Markers were designed to amplify putative exons from candidate genes. Standard PCR conditions were identified, and specific cDNA libraries were determined to contain cDNA clones of interest. Then, the markers were used to screen the arrayed library. Positive addresses indicating the presence of cDNA clones were confirmed by a second PCR using the same markers.  
20 Once a cDNA library was identified as likely to contain cDNA clones corresponding to a transcript of interest from the disorder critical region, it was used to isolate one or more clones containing cDNA inserts. This was accomplished by a modification of the standard "colony screening" method (Sambrook et al., 1989). Specifically, twenty 150 mm LB plus ampicillin agar  
25 plates were spread with 20,000 cfu of cDNA library. Colonies were allowed to grow overnight at 37°C. Colonies were then transferred to nylon filters (Hybond from Amersham-Pharmacia, Piscataway, NJ, or equivalent). Duplicates were prepared by pressing two filters together essentially as described (Sambrook et al., 1989). The "master" plate was then incubated  
30 another 6-8 hr to allow for additional growth. The DNA from the bacterial colonies was then bound to the nylon filters by treating the filters sequentially

with denaturing solution (0.5 N NaOH, 1.5 M NaCl) for 2 min, and neutralization solution (0.5 M Tris-Cl pH 8.0, 1.5 M NaCl) for 2 min. This was performed twice. The bacterial colonies were removed from the filters by washing the filters in a solution of 2 X SSC/2% SDS for 1 min while rubbing with tissue  
5 paper. The filters were air-dried and baked under vacuum at 80°C for 1-2 hr to crosslink the DNA to the filters.

cDNA hybridization probes were prepared by random hexamer labeling (Fineberg and Vogelstein, 1983, *Anal. Biochem.*, **132**:6-13). For small fragments, gene-specific primers were included in the reaction, and random  
10 hexamers were omitted. The colony membranes were then pre-washed in 10 mM Tris-Cl pH 8.0, 1 M NaCl, 1 mM EDTA, and 0.1% SDS for 30 min at 55°C. Following the pre-wash, the filters were pre-hybridized at 42°C for 30 min. Prehybridization solution (> 2 ml/filter) contained 6 X SSC, 50% deionized formamide, 2% SDS, 5 X Denhardt's solution, and 100 mg/ml denatured  
15 salmon sperm DNA. Filters were then transferred to hybridization solution containing denatured  $\alpha$ -<sup>32</sup>P-dCTP-labeled cDNA probe, and hybridized overnight at 42°C. Hybridization solution included 6 X SSC, 2% SDS, 5 X Denhardt's, and 100 mg/ml denatured salmon sperm DNA.

The following morning, the filters were washed in 2 X SSC and 2% SDS  
20 at room temperature for 20 min with constant agitation. Two more washes were performed at 65°C for 15 min each. A fourth wash was performed in 0.5 X SSC and 0.5% SDS for 15 min at 65°C. Filters were then wrapped in plastic wrap and exposed to radiographic film. Individual colonies from the plates were aligned with the autoradiograph. Positive clones were picked into a 1 ml  
25 solution of LB Broth containing ampicillin. After shaking at 37°C for 1-2 hr, aliquots of the solution were plated on 150 mm plates for secondary screening. Secondary screening was identical to primary screening (above) except that it was performed on plates containing ~250 colonies. This allowed individual colonies to be clearly identified. Positive cDNA clones were characterized by  
30 restriction endonuclease cleavage, PCR, and direct sequencing to confirm the sequence identity between the original probe and the isolated clone.

To obtain the full-length cDNA, novel sequence from the 5'-end of the clone was used to reprobe the library. The sequence of the probes were clone-dependent. Reprobing was repeated until the length of the cDNA cloned matched that of the mRNA, estimated by Northern analysis. Utilizing this  
5 process, a single uterus clone was isolated as clone Gene 216\_CS759. This clone was deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, VA 20110-2209 USA, under ATCC Designation No. PTA-3173, on March 14, 2001, according to the terms of the Budapest Treaty.

10 The uterus clone (SEQ ID NO:3) contained the entire Gene 216 open reading frame. Both strands of this clone were completely sequenced and the data were compared against the BAC sequence. Any discrepancies were flagged, and these regions were resequenced. Final analysis revealed that the uterine clone was 3433 bp long and contained the full complement of exons  
15 defining the open reading frame of Gene 216 (SEQ ID NO:3). In addition, the uterine clone contained a small portion of the Gene 216 5' untranslated region (5 bp), the entire 3' untranslated region with a polyadenylation signal, and a poly(A)+ tail of 76 bp in length. The Gene 216 open reading frame was determined to be 2436 bp in length and to encode a protein of 812 amino acids  
20 (SEQ ID NO:363). Analysis of the composition of SNPs across the cDNA clone revealed that it contained the most frequent haplotype (Figure 8, see below).

Rapid Amplification of cDNA ends (RACE) was performed following the manufacturer's instructions using a Marathon cDNA Amplification Kit  
25 (CLONTECH). This method was used to clone the 5' and 3' ends of candidate genes. cDNA pools were prepared from total RNA by performing first strand synthesis. For first strand synthesis, a sample of total RNA sample was mixed with a modified oligo (dT) primer, heated to 70°C, and cooled on ice. The sample was then incubated with 5 X first strand buffer (CLONTECH), 10 mM  
30 dNTP mix, and AMV Reverse Transcriptase (20 U/μl). The reaction mixture was incubated at 42°C for 1 hr, and then placed on ice.

For second-strand synthesis, the components were added directly to the reaction tube. These included template, 5 X second-strand buffer (CLONTECH), 10 mM dNTP mix, sterile water, and 20 X second-strand enzyme cocktail (CLONTECH). The reaction mixture was incubated at 16°C  
5 for 1.5 hr. T4 DNA Polymerase was added to the reaction mixture and incubated at 16°C for 45 min. The second-strand synthesis was terminated with the addition of an EDTA/Glycogen mix. The sample was purified by phenol/chloroform extraction and ammonium acetate precipitation. The cDNA pools were checked for quality by analyzing on an agarose gel for size  
10 distribution.

Marathon cDNA adapters (CLONTECH) were then ligated onto the cDNA ends using the standard protocol recommended by the manufacturer. The specific adapters contained priming sites that allowed for amplification of either 5' or 3' ends, and varied depending on the orientation of the gene specific  
15 primer (GSP) that was chosen. An aliquot of the double stranded cDNA was added to 10 µM Marathon cDNA adapter, 5 X DNA ligation buffer, T4 DNA ligase. The reaction was incubated at 16°C overnight and heat treated to terminate the reaction. PCR was performed by the addition of the following to the diluted double stranded cDNA pool: 10 X cDNA PCR reaction buffer, 10 µM  
20 dNTP mix, 10 µM GSP, 10 µM AP1 primer (kit), 50 X Advantage cDNA Polymerase Mix.

Thermal cycling conditions were carried out at 94°C for 30 sec; followed by 5 cycles of 94°C for 5 sec, 72°C for 4 min, 5 cycles of 94°C for 5 sec; followed by 70°C for 4 min; followed by 23 cycles of 94°C for 5 sec; 68°C for  
25 4 min. The first round of PCR was performed using the GSP to extend to the end of the adapter to create the adapter primer-binding site. Following this, exponential amplification of the specific cDNA of interest was performed. Usually, a second, nested PCR was performed to provide specificity. The RACE product was analyzed on an agarose gel. Following gel excision and  
30 purification (GeneClean, BIO 101), the RACE product was cloned into pCTNR (General Contractor DNA Cloning System, 5' - 3', Inc.) and sequenced to verify



that the clone was specific to the gene of interest.

The 5' RACE technique was employed to identify the 5' untranslated region of Gene 216. Experiments were performed using lung mRNA and a primer that hybridized near the 5' end of the available sequence. The result of the experiment identified an additional 75 bp 5' of that present in the uterus cDNA clone (rt690; SEQ ID NO:351). This sequence was subsequently cloned and deposited with the ATCC (American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 USA), as clone Gene 216\_rt690, under ATCC Designation No.PTA-3172 on March 14, 2001, according to the terms of the Budapest Treaty.

Further attempts to extend the 5' end of Gene 216 by 5' RACE gave similar results indicating that the 5' end of the transcript was obtained.

This sequence in combination with the uterus cDNA clone yielded the master consensus sequence containing the 5' to 3' cDNA for Gene 216 (SEQ ID NO:1; Figure 24).

2. Identification of Splice Variants: Additional cDNA clones were isolated and determined to represent alternatively spliced variants of Gene 216. To ensure that all splice variants present in lung tissue were identified, an RT-PCR-based screening protocol was designed using multiple primer pairs spanning the entire gene. These amplicons produced PCR fragments of approximately 600 bp and overlapped by approximately 100 bp. The PCR products were fractionated on agarose gels and any fragments that were different from the expected size were cloned and sequenced. The results are summarized in Figures 9 and 10. The availability of the complete genomic sequence of BAC RPCI-11\_1098L22 enabled the intron/exon structure of Gene 216 (Figure 11) to be determined. Gene 216 was determined to contain 22 exons that spanned approximately 23.5 kb of genomic DNA.

Analysis of the sequence surrounding the intron/exon boundaries of Gene 216 indicated that the consensus splice sequence GT/AG was used in all cases (Table 4). However, in several of the cDNA clones, the use of an alternative splice site at the intron/exon boundary of exon V was observed.

The sequence CAGCAG was observed at the border of intron UV and exon V.

The CAGCAG sequence represented a duplication of the canonical acceptor splice consensus CAG. The CAG sequence is found in approximately 65% of all known acceptor splice sites. Where there is a duplication of the CAG sequence, the splicing machinery can utilize either AG sequence as an acceptor site. If the first AG (splice site 1) is used, the resulting sequence encodes an alanine. If the second AG (splice site 2) is used, this alanine is deleted. Accordingly, use of the first AG in the intron/exon boundary of exon V of Gene 216 produces a splice variant that encodes the amino acid sequence DPQADQVQM (Figure 12) (SEQ ID NO:60). Use of the second AG produces a splice variant that encodes the amino acid sequence DPQDQVQM (Figure 12) (SEQ ID NO:61).

It is noted that the percentage of clones that used splice site 1 or splice site 2 could not be accurately determined from the dataset because the majority of the clones were derived from PCR-based techniques. Typically, there is bias in PCR reactions that results in the amplification of one splicing product over another. The amplified products, once cloned, may not reflect the true percentage of splicing products in the total population. For example, small splicing products are preferentially amplified over larger ones, and the loss or gain of an exon will skew the relative ratio of one splicing product to another.

**TABLE 4**

EXON	5' INTRON	5' EXON	5' EXON	5' INTRON
A		AAG	GTGAGG	
B	CAG	GAC	CCG	GTCAAT
C	CAG	GTG	CGA	GTGAGT
D	CAG	CAG	ACG	GTGAGA
D (ALT)	CAG	CAG	GAG	GTACGC
E	TAG	GAT	CAG	GTGAGC
F	TAG	TGG	AGG	GTGAGG
G	CAG	GGC	CTG	GTGAGG
H	CAG	TTG	CAG	GTGGGG
I	CAG	GTT	CAG	GTGGGT
J	CAG	GGG	ACG	GTGAGG
K	CAG	GAC	CGG	GTACGC
L	TAG	GCA	CAG	GTTAAG
M	CAG	GAG	CTG	GTGAGG
N	CAG	CTG	CTG	GTGAGA
O	CAG	GCT	GAG	GTAGGG
P	CAG	GGA	ATG	GTGAGG
P (ALT)	TAG	ATG	ATG	GTGAGC
Q	TAG	GTG	GGG	GTGAGA
R	CAG	GTT	AAA	GTATGC
S	CAG	ACG	TGG	GTARGC
T	CAG	GCG	TGG	GTGAGT
U	CAG	ACG	AAG	GTAGGC
V	CAG	CAG		

C85 A100 G100 N A84 G72 G100 T100 A82 A88 G84 T55

3. Promoter Analysis: In order to identify the transcriptional start site of Gene 216, multiple 5' RACE products were sequenced from several different tissues. In most cases the 5' ends were located 80 bp upstream of the translational start site. The region upstream of this sequence was then  
5 analyzed for potential transcription factor binding sites using GEMS Launcher, a promoter analysis program (Genomatix, Munich, Germany). GEMS Launcher uses statistically weighted algorithms to identify binding elements that comprise a promoter or regulatory module. A stretch of DNA sequence spanning 2000 bp upstream of the translational start site was analyzed. The  
10 results indicated that Gene 216 did not possess a TATA or CCAAT box. In fact, the first binding element that was identified was a GC box within the 5' untranslated region oriented in the opposite direction (Figure 13). This result is not unprecedented since 60% of TATA-less genes possess a GC box on the opposing strand. Also, this result was in agreement with published data  
15 regarding the promoters of mouse ADAM 17 and 19. Other binding elements that were identified within 600 bp upstream of the initiator methionine included an E-box, one AP2, and three SP1 sites (Figure 13). These types of binding elements were also identified in the mouse ADAM 17 and 19 genes, and may represent components of a promoter module for Gene 216. Approximately  
20 1200 bp upstream of the putative promoter module, GEMS Launcher identified binding elements that may comprise an additional regulatory element (Figure 13). This region was highly conserved with the mouse ortholog of Gene 216 (see below), as determined by dot matrix analysis.

4. BLAST Analysis: BLASTP, BLASTN, and BLASTX analysis of  
25 Gene 216 against protein and nucleotide databases revealed that it was a novel member of the ADAM (A Disintegrin And Metalloprotease) gene family. The ADAM gene family is a sub-group of the zinc-dependent metalloprotease superfamily. There are currently 31 known members of the ADAM gene family. ADAM proteins have a complex domain organization that includes a signal  
30 sequence, a propeptide domain, a metalloprotease domain, a disintegrin domain, a cysteine-rich domain, and an epidermal growth factor-like domain,

as well as a transmembrane region and a cytoplasmic tail. ADAM proteins have been implicated in many processes, including proteolysis in the secretory pathway and extracellular matrix, extra- and intra-cellular signaling, processing of plasma membrane proteins, and procytokine conversion. The homology of  
5 Gene 216 and human ADAMs 19, 12, 15, 8 and 9 indicated that Gene 216 belonged to a branch of the 31-member family containing active metalloprotease domains (Figure 14).

5. Expression Analysis: To characterize the expression of Gene 216, a series of expression experiments were performed.
- 10 i. Northern Analysis: Northern analysis (Sambrook et al., 1989) of the Gene 216 transcript was performed. Probes were generated using one of the methods described below. Briefly, sequence verified IMAGE consortium cDNA clones were digested with appropriate restriction endonucleases to release the insert. The restriction digest was electrophoresed on an agarose  
15 gel and the bands containing the insert were excised. The gel piece containing the DNA insert was placed in a Spin-X (Corning Costar Corporation, Cambridge, MA) or Supelco spin column (Supelco Park, Bellefonte, PA) and spun at high speed for 15 min. DNA was ethanol precipitated and resuspended in TE.
- 20 Alternatively, products were purified from PCR or RT-PCR. First, oligonucleotide primers were designed for PCR amplification of portions of cDNA, EST, or genomic DNA. Pools of DNA (for PCR) or RNA (for RT-PCR) were used as template for the reactions. The PCR primers were used to amplify genomic DNA to verify the size of the predicted product. The expected  
25 size was based on the genomic sequence. Inserts purified from IMAGE clones or PCR products were random primer labeled (Fineberg and Vogelstein, *supra*) to generate probes for hybridization. Probes were labeled by incorporation of  $\alpha$ -<sup>32</sup>P-dCTP in second round of PCR. Commercially available Multiple Tissue Northern blots (CLONTECH, Palo Alto, CA) were hybridized and washed under  
30 conditions recommended by the manufacturer. A separate filter that contained 6 tissues from the immune system was also utilized (CLONTECH). The results

revealed a major 5.0 kb transcript and a minor 3.5 kb transcript that were expressed in most tissues examined (Figures 15A-15B). The strongest signals were consistently identified in heart, skeletal muscle, colon, lymph, and small intestine. Moderate expression levels were observed in lung, liver, kidney, placenta, bone marrow, and brain.

It was hypothesized that the 5 kb transcript was an incompletely spliced transcript from Gene 216. To test this hypothesis, Northern blotting was performed using cytoplasmic mRNA isolated from bronchial smooth muscle cells. The same radioactive probe was employed as described above. The results showed a very strong 3.5 kb signal and no signal at 5.0 kb (Figure 15C). This suggested that the predominant 5 kb transcript contained intronic material and was localized to the nucleus. Notably, intron ST is 1.4 kb in size. The addition of the ST intron to the 3.5 kb full length cDNA would produce a transcript that is ~5.0 kb in size. This suggests that regulatory elements in the region around intron ST affect splicing, retention in the nucleus, and/or transport to the cytoplasm.

ii. RNA Dot Blot Analysis: RNA dot blotting was used to determine the expression of Gene 216 in a wide range of tissues. mRNA from 50 tissues was dotted onto a nylon filter, and probed with a radiolabeled oligo designed to hybridize to the 3' untranslated region of Gene 216. Figure 16 shows that Gene 216 was highly expressed in gastrointestinal tissues as well as aorta, uterus, prostate, ovary, lung, fetal lung, trachea, and placenta. The majority of these tissues are derived from the endoderm. During development, the endoderm forms a tube that produces the primordium of the digestive tract. Extensions from this tube also develop into the lung and trachea.

iii. RT-PCR: Total RNA was isolated from primary cultures of seven cell types cultured from lung tissue. This RNA was analyzed in RT-PCR experiments. Genomic DNA was removed from the total RNA by DNaseI digestion. The "'Superscript' Preamplification System for First strand cDNA synthesis" (Life Technologies) was used according to the manufacturer's specifications. cDNA was synthesized from DNaseI treated total RNA using

oligo(dT) or random hexamers. Gene specific primers were used to PCR amplify the target cDNAs. The PCR reaction contained 0.5  $\mu$ l of first strand cDNA, 1  $\mu$ l sense primer (10  $\mu$ M), 1  $\mu$ l antisense primer (10  $\mu$ M), 3  $\mu$ l dNTPs (2 mM), 1.2  $\mu$ l  $MgCl_2$  (25 mM), 3  $\mu$ l 10 X PCR buffer, and 1 U Taq Polymerase (Perkin Elmer). Total volume was 30  $\mu$ l. The PCR reaction mixture was incubated at 94°C for 4 min; followed by 30 cycles of incubation at 94°C for 30 sec, 58°C for 1 min; followed by incubation at 72°C for 1 min; followed by a final incubation at 72°C for 7 min. PCR products were analyzed on agarose gels. Figure 17 shows that Gene 216 was expressed in lung fibroblasts, pulmonary artery smooth muscle cells, bronchial smooth muscle cells and total lung, but was not expressed in bronchial epithelium or pulmonary artery endothelial cells.

iv. cDNA Library Representation: A comprehensive approach to determining the tissue distribution of Gene 216 was performed by *in silico* data mining. For searches, public EST database and Genome Therapeutics Corporation's internal cDNA database were used. BLASTN2 analysis identified ESTs from multiple cDNA libraries. A summary of all tissues expressing Gene 216 is given in Table 5.

**TABLE 5**

Source	Tissue
UNIGENE	Eye Muscle Placenta Stomach Uterus Whole embryo Breast Normal testis
Direct selected cDNAs	Bronchial smooth muscle (1 clone) Normal lung (2 clones) Brain (1 clone)
Primary cell types (RT/PCR)	Pulmonary artery smooth muscle Bronchial smooth muscle Lung fibroblast Total lung
RNA Dot Blot	Aorta Colon

	Bladder Uterus Prostate Ovary Small intestine Heart Stomach Testis Appendix Lung Trachea Fetal kidney Fetal lung
Northern Blot	Brain Heart Skeletal muscle Colon Thymus Spleen Kidney Liver Small intestine Placenta Lung Lymph Bone marrow

#### **EXAMPLE 8: Gene 216 Polypeptide**

1. ADAM Family Features: The zinc-dependent metalloprotease superfamily is comprised of several sub-groups. Metalloproteases that exhibit the zinc-binding consensus sequence HEXXHXXGXXH (SEQ ID NO:62) are referred to as zincins. In zincins, the 3 histidines in the consensus sequence play an essential role in binding to the zinc ion. Such binding is essential for catalytic activity. Zincins can be further divided into metzincins, which contain a methionine residue beneath the active-site zinc ion ("Met-turn" motif). Within this sub-group there are 4 sub-families: astacins, matraxins, adamlysins, and serralysins. The ADAM proteins belong to adamlysins sub-family of metzincins, along with snake venom metalloproteases.

Currently, there are 31 known members of the ADAM family. The ADAM genes encode proteins of approximately 750 amino acids that contain 8 different domains. Domain I is the pre-domain and contains the signal

sequence peptide that facilitates secretion through the plasma membrane. Domain II is the pro-domain that is cleaved before the protein is secreted resulting in activation of the catalytic domain. Domain III is the catalytic domain containing metalloprotease activity. Domain IV is the disintegrin-like domain that is believed to interact with integrins or other receptors. Domain V is the cysteine-rich domain and is speculated to be involved in protein-protein interactions or in the presentation of the disintegrin-like domain. Domain VI is the EGF-like domain that plays a role in stimulating membrane fusion. Domain VII is the transmembrane domain that anchors the ADAM protein to the membrane. Domain VIII is the cytoplasmic domain that contains binding sites for cytoskeletal-associated proteins and/or SH3 binding domains. This binding is thought to play a role in bi-directional signaling. Figure 8 shows the location of the ADAM domains identified in the Gene 216 protein sequence.

To determine whether Gene 216 was a novel member of the ADAM family, the 812 amino acid sequence was aligned with other ADAM proteins using Pile-Up (Genetics Computer Group, Burlington, MA) (Figure 18). Sequence alignments indicated that the Gene 216 protein contained the eight domains characteristic of ADAM proteins (Figure 18). The consensus sequence HEXXHXXGXXH (SEQ ID NO:62) was located within the catalytic domain of Gene 216 protein. In addition, a methionine residue identified as a "Met-turn" was located in the Gene 216 protein. A conserved cysteine (amino acid 133) was identified in the prodomain of Gene 216 protein. This cysteine is important for activation in other ADAMs, as it forms an intramolecular complex with the zinc ion bound to the metalloprotease domain. The cysteine-zinc complex blocks the active site, and dissociation of the cysteine is required for catalytic activity. Dissociation is believed to activate the catalytic domain by a conformational change or the enzymatic cleavage of the prodomain. This process is referred to as the "cysteine switch".

In ADAM 12, the conserved cysteine is located at a different position than conserved cysteines in other ADAM proteins (B.L. Gilpin et al., 1998, *J. Biol. Chem.* **273**:157-166). This alternative position correspond to amino acid



179 in Gene 216 (Figure 19). However, sequence analysis of 14 ADAMs, including ADAMs 8, 9, 12 and 15 (Stone et al., 1999, *J. Prot. Chem.* **18**:447-465) made it more likely that position 133 of Gene 216 was involved in the cysteine switch (see Figures 18 and 19) . In addition, Gene 216 shared a higher percentage of sequence identity with other ADAMs around position 133 than position 179. This provided further support that the Gene 216 cysteine at position 133 was involved in the cysteine switch.

Hydrophobicity analysis (PepPlot, Genetics Computer Group) of the Gene 216 amino acid sequence revealed the presence of two hydrophobic regions (Figure 20). One region was located at the amino terminus of the protein and contained the predicted the signal sequence. The other hydrophobic region was located near the carboxyl terminus and contained the predicted transmembrane domain that anchors the protein to the cell surface. Computational biology analysis (BLIMPS, Henikoff et al., 1994, *Genomics* **19**:97-107) of the Gene 216 cytoplasmic domain revealed the presence of a putative SH2 and SH3 binding domain as well as a putative casein kinase I phosphorylation site (Figure 19). Such sites may contribute to the bi-directional signaling of Gene 216, as observed for other ADAM proteins.

Sequence analyses indicated that Gene 216 is a novel member of the ADAM family. Gene 216 is most closely related to ADAMs 8, 9, 12, 15, and 19, a branch of the family that is known to possess an active metalloprotease domain. Table 6 lists the 5 most similar BLASTP hits using the Gene 216 amino acid sequence as a query. In humans, Gene 216 is most closely related to ADAM 19. Based on BLASTN and BLASTP analysis, Gene 216 nucleotide sequence shares the 37% identity with the ADAM 19 nucleotide sequence; and Gene 216 amino acid sequence shares 58% identity with the ADAM 19 amino acid sequence.

**TABLE 6: Top 5 Hits from BLAST Analysis of Gene 216 protein**

Hit	GenBank Locus	Description	Smallest Sum
1	U66003	<i>Xenopus laevis</i> (ADAM 13)	5.5e-166

5	2	AF019887	<i>Mus musculus</i> metalloprotease-disintegrin meltrin beta	1.2e-139
	3	AF134707	<i>Homo sapiens</i> disintegrin and metalloprotease domain 19 (ADAM19)	1.6e-139
	4	S60257	Mouse mRNA for meltrin alpha	1.8e-121
10	5	AF023476	<i>Homo sapiens</i> meltrin-L precursor (ADAM12)	4.9e-119

Table 7 lists the top two hits from BLIMPS analysis of the Block protein motif database.

**TABLE 7: Top 2 Hits from BLIMPS Analysis of Gene 216 protein**

15	Description	Strength Score	AA#	AA
	Disintegrins proteins	1950	1597	377
<u>Sequence:</u> CCfAhnCsLRPGAQCAhGdCCvRCllKpAGaICRqAMGDCDIPEfCTGTSShCPP (SEQ ID NO:335)				

20	Description	Strength Score	AA#	AA
	Zinc metalloproteinases	1173	1276	276
<u>Sequence:</u> TMAHEIGHSLG (SEQ ID NO:336)				

25

2. Amino Acid Changes: Table 10 below lists the SNPs identified in Gene 216. A total of 53 SNPs are disclosed. In total, 9 SNPs were identified in the Gene 216 open reading frame. The remaining SNPs do not affect the resulting protein, however, they can affect the expression and resulting phenotype. Example 10 describes SNP identification for Gene 216, and Figure 19 shows resulting changes to the protein sequence. Seven of the nine SNPs caused amino acid changes in the Gene 216 protein. The other 2 SNPs comprised silent mutations. Of the 7 amino acid changes, 4 were clustered toward the carboxyl terminus of the Gene 216 protein. One SNP was identified in the Gene 216 transmembrane domain, while 3 SNPs were

identified in the cytoplasmic domain.

Of the cytoplasmic tail SNPs, one was located in an SH2 binding domain. This SNP caused a non-conservative amino acid change: methionine (hydrophobic) to threonine (polar). The other two cytoplasmic tail SNPs also  
5 caused non-conservative amino acid changes: proline (hydrophobic) to serine (polar) and glutamine (polar) to histidine (basic). Such changes can disturb the signaling properties of the Gene 216 protein. In addition, the transmembrane domain SNP caused an amino acid change from valine to isoleucine. This change can affect Gene 216 signaling efficiency.

10 The two SNPs in the Gene 216 pro-domain generated non-conservative amino acid changes: tyrosine (polar) to histidine (basic) and threonine (polar) to alanine (hydrophobic). Since the ADAM pro-domain is cleaved during activation of the catalytic domain, such changes may affect the cleavage process. One SNP in the Gene 216 catalytic domain resulted in a change from  
15 alanine (hydrophobic) to valine (hydrophobic). This change can affect the sheddase (i.e., proteolysis) efficiency of the protein.

Notably, amino acid changes in the identified Gene 216 catalytic domain, especially within the metalloprotease domain, is important as this domain is critical to sheddase function. Recently, the X-ray crystallographic  
20 data of the snake venom catalytic domain was determined and deposited in the public domain (Protein Data Bank web site, Research Collaboratory for Structural Bioinformatics (RCSB) Consortium, Rutgers University, Piscataway, NJ; Accession No. 1C9GA). This information can be utilized to predict whether an amino acid change will alter the folding of the catalytic domain of the Gene  
25 216 protein. In particular, the sequence of the catalytic domain of Gene 216 protein can be plotted as X-ray crystallographic coordinates and used to determine changes in the tertiary structure of this domain.

3. Biological Role of Gene 216: ADAM proteins belong to a part of a very large superfamily of zinc-dependent metalloproteases (Stone et al.,  
30 1999, *J. Prot. Chem.* **18**:447-465). Gene 216 represents a novel member of the ADAM family that is closely related to ADAM 19. ADAM 19 is known to

participate in the proteolytic processing of the membrane anchored protein neuregulin 1 (NRG1) (Shirakabe et al., 2001, *J. Biol. Chem.* **276**(12):9352-8).

The expression and activation of ADAM 19 protein is localized to the trans-golgi apparatus. This localization has also been observed for other ADAM  
5 proteins (Lum et al., 1998, *J. Biol. Chem.* **273**:26236-26247; Roghani et al., 1999, *J. Biol. Chem.* **274**:3531-3540; Shirakabe et al., 2001, *J. Biol. Chem.* **276**(12):9352-8). This suggests that the ADAM genes, including Gene 216, encode proteins that function in the trans-golgi apparatus as intracellular processing enzymes. The processed substrates of these enzymes may be  
10 released into the cytosol as part of a signal transduction cascade that leads to the cell surface.

The substrate of ADAM 19 is termed NRG1. NRG1 belongs to a group of growth and differentiation factors (neuregulins) that bind to members of the EGF family of tyrosine kinase receptors. Data suggest that the proteolytically  
15 cleaved isoform of NRG1, NRG- $\beta$ 1, may induce the tyrosine phosphorylation of EGFR2 and EGFR3 in differentiated muscle cells (Shirakabe et al., 2001, *J. Biol. Chem.* **276**(12):9352-8). The sequence similarity of Gene 216 protein and ADAM 19 protein suggests that neuregulins or their isoforms serve as substrates for Gene 216 protein. Gene 216-processed neuregulins or isoforms  
20 can serve as ligands for EGFR1. Although other researchers have not demonstrated expression of neuregulins in lung tissue, Northern blots and RT/PCR experiments performed in accordance with this invention showed that NRG2 is expressed at low levels in lung tissue (data not shown).

Epidermal growth factor receptor (EGFR1) plays a pivotal role in the  
25 maintenance and repair of epithelial tissue. Following injury in bronchial epithelium, EGFR1 is upregulated in response to ligands acting on it or through transactivation of the EGFR1 receptor. This results in increased proliferation of cells and airway remodeling at the point of insult, and leads to the repair of the bronchial epithelium (Polosa et al., 1999, *Am. J. Respir. Cell Mol. Biol.* **20**:914-923; Holgate et al., 1999, *Clin. Exp. Allergy Suppl* **2**:90-95).  
30

In asthma, the bronchial epithelium is highly abnormal. Structurally, the

columnar cells separate from their basal attachments. Functionally, there is increased expression and release of proinflammatory cytokines, growth factors, and mediator-generating enzymes. Beneath this damaged structure, subepithelial myofibroblasts are activated to proliferate. This proliferation  
5 causes excessive matrix deposition leading to abnormal thickening and increased density of the subepithelial basement membrane.

Immunocytochemical studies have shown that both TGF-  $\beta$  and EGFR1 are highly expressed at the area of injury. This suggests that parallel pathways operate in the repair of epithelial cells (Puddicombe et al., 2000, *FASEB J.*  
10 **14**:1362-1374). It is postulated that EGFR1 stimulates epithelial repair, while TGF-  $\beta$  regulates the production of profibrogenic growth factors and proinflammatory cytokines that lead to extracellular matrix synthesis. Notably, EGFR1 is involved in regulating a number of different stages of epithelial repair, e.g., survival, migration, proliferation, and differentiation. Accordingly,  
15 dysregulation of EGFR1 may cause the epithelium to arrest in a "state of repair" (Holgate et al., 1999, *Clin. Exp. Allergy Suppl* **2**:90-95).

Thus, Gene 216 protein and its variants can induce the epithelium into a continuous state of repair by functioning improperly, e.g., failing to bind, process, or release its substrate. The Gene 216 substrate may be a member  
20 of the neuregulin family that serves as the ligand for EGFR1. The decrease in processed neuregulin-type substrate could, in turn, cause the observed increase in EGFR1 expression. At the same time, the TGF-  $\beta$  pathway could remain active. This would be expected to produce a continuous source of proinflammatory factors as well as growth factors. Overproduction of these  
25 factors could act to drive airway wall remodeling causing bronchial hyperresponsiveness, a phenotype of asthma.

It is also possible that the disintegrin-like domain of Gene 216 plays a role in respiratory diseases such as asthma. Integrins are a family of heterodimeric transmembrane receptors that mediate cell-cell and cell-  
30 extracellular matrix interaction (Hynes, 1992, *Cell* **69**:11). Integrins promote angiogenesis (Brooks et al., 1994, *Science* **264**:569), which plays a major role

in various pathological mechanisms, such as tumor growth, metastasis, diabetic retinopathy, and certain inflammation diseases (Folkman, 1995, *N. Engl. J. Med.* **333**:1757). Disintegrins act as integrin ligands that disrupt cell-matrix interactions (C.P. Blobel and J.M. White, 1992, *Curr. Opin. Cell Biol.* **4**:760-5) and inhibit angiogenesis (C.H. Yeh et al., 1998, *Blood* **92**:3268-3276).

Thus, the disintegrin-like domain of the Gene 216 polypeptide can inhibit angiogenesis in the respiratory system. Gene 216 variants that have partly functional or non-functional disintegrin activity may lack anti-angiogenesis function. These Gene 216 variants may give rise to angiogenesis and inflammation in the respiratory system, a phenotype of asthma.

#### **EXAMPLE 9: Identification of the Mouse Homolog for Gene 216**

The mouse ortholog of Gene 216 was identified by TBLASTN analysis of Gene 216 against mouse dbEST (NCBI). BLAST analysis identified three mouse ESTs that were partially homologous to the human sequence but were not 100% identical to any known mouse ADAM genes. However, three mouse ESTs were 100% identical to a partially sequenced mouse BAC (BAC389B9; Accession Number AF155960). This BAC maps to mouse chromosome 2 in a region that is syntenic to human chromosome 20p13. The 47 kb BAC sequence was analyzed for potential genes using the Genscan gene prediction program (Burge and Karlin, *J. Mol. Biol.*, **268**:78-94). Additional putative exons were identified based on comparison of the human Gene 216 protein to the mouse BAC by TBLASTN. The results identified a mouse gene that contained an ORF of 2124 bp encoding a protein of 707 amino acids. The genomic nucleotide sequence of the mouse homolog is depicted in Figure 21 and the corresponding amino acid sequence is depicted in Figure 22. The mouse amino acid sequence was analyzed by BLASTP analysis and found to have homology to mouse and human ADAM proteins. The mouse amino acid sequence was aligned against the amino acid sequence of human Gene 216 (BestFit, Genetics Computer Group; Figure 23). The results indicated that the mouse and human proteins shared ~70% identity at the amino acid level. This

confirmed that the mouse sequence was the murine ortholog of human Gene 216.

**EXAMPLE 10: Polymorphism Identification**

Polymorphisms were identified in the chromosome 20 region and subsequently used in association studies. Most of the data focused on the region of Gene 216.

1. Single Nucleotide Polymorphism (SNP) Discovery: An efficient multi-tiered approach was used for mutation analysis. First, PCR assays were performed to analyze exons and the consensus splice sites. Assays were designed for all exons that contributed to the open reading frame of the gene. This strategy ensured the detection of mutations that modified the protein sequence as well as mutations that were predicted to disrupt mRNA splicing. The identified promoter and putative regulatory element for Gene 216 and a large intronic region were assayed for polymorphisms as well. Second, a total of 77 individuals were tested for polymorphisms using fluorescent SSCP (single strand conformational polymorphism). This sample size provided a 99% power to detect a polymorphism with a frequency of 3% or greater. Briefly, PCR was used to generate templates from asthmatic individuals that showed increased sharing for the 20p13-p12 chromosomal region and contributed towards linkage. Non-asthmatic individuals were used as controls. Enzymatic amplification of Gene 216 was accomplished using PCR with oligonucleotides flanking each exon as well as the putative 5' region. Primers were chosen to amplify each exon as well as 15 or more base pairs within each intron on either side of the splice site. The forward and the reverse primers were labeled with two different dye colors to allow analysis of each strand and confirm variants independently. Standard PCR assays were utilized for each exon primer pair following optimization. Buffer and cycling conditions were specific to each primer set. The products were denatured using a formamide dye and electrophoresed on non-denaturing acrylamide gels with varying concentrations of glycerol (at least two different glycerol concentrations).

Primers utilized in fluorescent SSCP experiments to screen coding and

non-coding regions of Gene 216 for polymorphisms are provided in Table 8. Column 1 lists the genes targeted for mutation analysis. Column 2 lists the specific exons analyzed. Column 3 lists the primer names. Columns 4 and 5 list the forward primer sequences and corresponding SEQ ID NOS, respectively. Columns 5 and 6 list the reverse primer sequences and corresponding SEQ ID NOS, respectively.

Once polymorphisms were identified, multiple individuals representative of each SSCP pattern and two genomic controls were sequenced. Sequencing was used to validate polymorphisms and to identify SNPs. The variants detected in the initial set of asthmatic and normal individuals were subject to fluorescent sequencing (ABI) using a standard protocol described by the manufacturer (Perkin Elmer). In cases where SSCP did not identify polymorphisms in Gene 216, sequence information was obtained from 16 individuals that were identical by descent (IBD) in the region, and from 4 controls. This was done to ensure that all potential polymorphisms were identified.

Primers utilized in DNA sequencing for purposes of confirming polymorphisms detected using fluorescent SSCP are provided in Table 9. Column 1 lists the specific exons sequenced. Column 2 lists the forward primer names, column 3 lists the forward primer sequences, and column 4 lists the corresponding SEQ ID NOS. Column 5 lists the reverse primer names, column 6 lists the reverse primer sequences, and column 7 lists the corresponding SEQ ID NOS.

Single nucleotide polymorphisms (SNPs) that were identified in Gene 216 are provided in Table 10. Column 1 lists the SNP numbers (1-53). Column 2 lists the exons that either contain the SNPs or are flanked by intronic sequences that contain the SNPs. Column 3 lists the PMP sites for the SNPs. A "-" denotes polymorphisms which are 5' of the exon that are within the intronic region. The corresponding number is given from the 3' to 5' direction. A "+" denotes polymorphisms which are 3' of the exon that are within the intronic region. The number corresponding to the "+" is given from the 5' to 3'



direction. Columns 2 and 3, combined, show the SNP names as described herein, e.g., T+1, T+2, etc. Column 4 indicates whether the SNP was detected in an exon or intron sequence. Column 5 lists the SNP locations in the Gene 216 genomic sequence of SEQ ID NO:6 (see Figure 7). Column 6 lists the

5 SNP reference sequences which illustrate the SNP nucleotide changes with underlining. Column 7 lists the SEQ ID NOs of the SNP reference sequences. Column 8 lists the base changes of the SNP sequences. Column 9 lists the amino acid changes resulting from the SNP sequences.

It is noted that the SNP nomenclature from related U.S. Application

10 Serial Number 09/834,597, filed April 13, 2001, has been revised in this continuation-in-part application. The table describing the former and present SNP nomenclature is shown immediately following Table 10, below.

TABLE 8

Gene	Exon	Assay Name	Primer Sequence	SEQ ID NO:	Primer Sequence	SEQ ID NO:
216	216_AA	1619_216_AA_F_1620_216_AA_R	acaagagaccttaacgca		ttcgagcagtgagagaaacct	
216	216_A	502_216_A_F_503_216_A_R	ctgctcagagggccgagga	63	agctctgagcagaccattc	106
216	216_A	1623_216_A_F_1624_216_A_R	caggagaccacggagatcg	64	ctcgaggggttgagctg	107
216	216_A	1625_216_A_F_1626_216_A_R	ttgctgaaccttctatcc	65	gagaggaggagagaacogct	108
216	216_B	293_216_B_F_294_216_B_R	ccctgtgtcttcaggctc	66	agtgactgtgtgtctggg	109
216	216_C	295_216_C_F_296_216_C_R	gcctcacactttttctgcc	67	tgtcatctgcacctctctg	110
216	216_D	297_216_D_F_298_216_D_R	aggcaggaggaaagtgaat	68	aagaggagggtgtgtgtagg	111
216	216_E	1290_216_E_F_1291_216_E_R	cctaccacacctctctt	69	gltatcaggccactagggtg	112
216	216_F	299_216_F_F_300_216_F_R	cctaacctctgcacctta	70	atatagcattccactccca	113
216	216_G	301_216_G_F_302_216_G_R	aacttctcttggaagtgg	71	gaaggcgagaattccogt	114
216	216_H	700_216_H_F_701_216_H_R	cacacctgtgtgaggagaga	72	caccagcaccctgcctctc	115
216	216_I	305_216_I_F_306_216_I_R	ccacgaaggaccacog	73	gggtcagaggccaccac	116
216	216_J	889_216_J_F_890_216_J_R	ctacgtgtgtgtgctctg	74	gccgtagagctctctgtct	117
216	216_K	891_216_K_F_892_216_K_R	ctctacggccgcagtgac	75	gacgaccaaagaacacgcag	118
216	216_L	311_216_L_F_312_216_L_R	gtccctcatgcccacatg	76	tgagcggagaggggcaagt	119
216	216_M	313_216_M_F_314_216_M_R	caggttaagtgtgctgc	77	aaacctcacacctgaacct	120
216	216_N	315_216_N_F_316_216_N_R	ctctctctgctctccac	78	aagggtgctgtgtctctct	121
216	216_O	317_216_O_F_318_216_O_R	tctactgtgggaagatggg	79	ccactcagctccactcccta	122
216	216_P	319_216_P_F_320_216_P_R	ccctctactctctccca	80	ggattcaacggcgaagag	123
216	216_R	321_216_R_F_322_216_R_R	gaccttgggttctatctcc	81	gtctagctcttgacaggttg	124
216	216_S	323_216_S_F_504_216_S_R	gtgcacctctcaggacac	82	gaaccgcaggagtaggtctc	125
216	216_T	325_216_T_F_326_216_T_R	cttggactctatcacgttgc	83	atatgttcagcagagatccc	126
216	216_U	327_216_U_F_328_216_U_R	ttaacctcacactttctcc	84	gcatactgtctctcatgataa	127
216	216_U	1308_216_U_F_1309_216_U_R	gtggagaggaggaggagaag	85	gaggctttgaatccaggctcc	128

216	216_V	1294_216_V_F_1295_216_V_R	ccccatgggtgaatttaca	86	cagcaagacacacgcacatcac	129
216	216_V	1296_216_V_F_1297_216_V_R	gcagctagccttaccagttaca	87	gggacagagggaaaccttfta	130
216	216_V	1298_216_V_F_1299_216_V_R	accacgcctatagccaacat	88	ttctctctgtttcttcca	131
216	216_V	1300_216_V_F_1301_216_V_R	aggtctagcacctggattgg	89	gtcctggagctgtgtgtgt	132
216	216_V	1302_216_V_F_1303_216_V_R	ccccaggaccactagctct	90	aggaaaccacagagccacacia	133
216	216_V	1304_216_V_F_1305_216_V_R	attgagctggagagtgcc	91	ttcctctgtgagaggttagc	134
216	216_V	1306_216_V_F_1307_216_V_R	ttcaagttctctggatggct	92	ttcctggatcacctgttcttc	135
216	216_AA	1619_216_AA_F_1620_216_AA_R	acaagaccctctaaacgca	93	ttcagcagctggagaaacct	136
216	216_RS	1465_216_RS_F_1466_216_RS_R	acctctgtgacaagccag	94	ctgggagctggtagcaaca	137
216	216_ST	1467_216_ST_F_1468_216_ST_R	gttgtctaccgactccacag	95	aggccactggaaacctct	138
216	216_ST	1469_216_ST_F_1470_216_ST_R	cccaggctgacagagcag	96	gcagcaltgtacagggaactg	139
216	216_ST	1471_216_ST_F_1472_216_ST_R	gtctctctgttccactctct	97	cagctgacacagtggtatgga	140
216	216_ST	1473_216_ST_F_1474_216_ST_R	ggcaacttctctgcacaaat	98	tgtcagacatggccacagag	141
216	216_ST	1475_216_ST_F_1476_216_ST_R	ttctctgtgaccctgggtgt	99	agggtctcttagctgcccac	142
216	216_ST	1477_216_ST_F_1478_216_ST_R	atttgggccagagatggg	100	aggcctgttcatttctctgtg	143
216	216_ST	1479_216_ST_F_1480_216_ST_R	ggcagagggagcaagtggtg	101	caagaacacctggatgtccg	144
216	216_ST	1481_216_ST_F_1482_216_ST_R	atggctfggaatcatcaagg	102	ctcagctccctctctcttc	145
216	216_ST	1483_216_ST_F_1484_216_ST_R	tagagagaggggtgcccagc	103	ctgtgtgggccatcttftg	146
216	216_TU	1485_216_TU_F_1486_216_TU_R	aaagatggccacacacagg	104	ggagaaatgtgtggagggtaa	147
216	216_UV	1487_216_UV_F_1488_216_UV_R	agaactctcatgagcccagc	105	aagccacacagcttctctct	148
216	216_UV	1489_216_UV_F_1490_216_UV_R	aggttcttgggctcaggfta	149	caggtatcttggcatctggac	153
216	216_QR	1463_216_QR_F_1464_216_QR_R	gttaggtgtgcccagagcagg	150	ctggctgtgtcacagaagggt	154
216	216_Q	1292_216_Q_F_1293_216_Q_R	tgtggacctagatgtgtgagc	151	ctggagcacagtggcagfta	155
216	216_KL	1736_216_KL_F_1737_216_KL_R	caaagtcacacacaacagcgg	152	tttgtgtgtcttcagtttc	156

TABLE 9

Exon	Forward	Forward Seq	SEQ ID NO:	Reverse Name	Reverse Seq	SEQ ID NO:
216 A	MDSeq 101 216 A F	cctctagagtagagggccc	157	MDSeq 101 216 A R	ccaagcacactttagcgtc	177
216 A	MDSeq 175 216 A F	agcggtctctctctctc	158	MDSeq 175 216 A R	agcactgccctctgcttt	178
216 A	MDSeq 213 216 A F	cctctagagtagagggccc	159	MDSeq 213 216 A R	cagccaagcacacttga	179
216 A	MDSeq 334 216 A F	atgttactgagggccgaaggg	160	MDSeq 334 216 A R	cccatagctgttagctctc	180
216 B	MDSeq 296 216 B F	ccctttcagcctctctt	161	MDSeq 296 216 B R	aaagctttaggaaccaca	181
216 C	MDSeq 297 216 C F	caggagctgaacaatcctga	162	MDSeq 297 216 C R	atcttggtccctgcatc	182
216 D	MDSeq 61 216 D F	tccctgtgtctccata	163	MDSeq 61 216 D R	gaggagctctttcccca	183
216 E	MDSeq 245 216 E F	agcgaggaggagcgtgaat	164	MDSeq 245 216 E R	ggaccaccaggaggcgtg	184
216 F	MDSeq 57 216 F F	cctctgcccctcttct	165	MDSeq 57 216 F R	aacccacgctccaggaag	185
216 G	MDSeq 336 216 G F	ccgaaatgccagagctctga	166	MDSeq 336 216 G R	ctgtcaccttggaagggaac	186
216 H	MDSeq 155 216 H F	ggcctcgagtcaccatatt	167	MDSeq 155 216 H R	actgcaggaggccacagag	187
216 I	MDSeq 363 216 I F	agagcctcctgtctctccct	168	MDSeq 363 216 I R	accyaaacttgaaccacacc	188
216 J	MDSeq 181 216 J F	tgcctcagctctctcag	169	MDSeq 181 216 J R	tgaggagacgaaccaagaac	189
216 K	MDSeq 182 216 K F	tccgttggtgtcctctga	170	MDSeq 182 216 K R	caaagtcacacacacagcg	190
216 L	MDSeq 106 216 L F	gggttaactccctctctgg	171	MDSeq 106 216 L R	gaacctgagggcaccaatfa	191
216 N	MDSeq 337 216 N F	ctgggcttccaccctgg	172	MDSeq 337 216 N R	tfggccttagttaattgtgc	192
216 O	MDSeq 338 216 O F	ctgggcttccaccctgg	173	MDSeq 338 216 O R	tfggccttagttaattgtgc	193
216 P	MDSeq 49 216 P F	tccagggtggaactctgc	174	MDSeq 49 216 P R	ctggagcacagtggaactfa	194
216 R	MDSeq 248 216 R F	tagaatgtgtgagctctgccc	175	MDSeq 248 216 R R	aggagtaggctctcaggagga	195
216 S	MDSeq 96 216 S F	gaacttgggtttctaattcc	176	MDSeq 96 216 S R	tgtacttgggaggttaggggc	196
216 T	MDSeq 50 216 T F	agagggtgacttgagcgaga	197	MDSeq 50 216 T R	ccagaaacctgattagggggg	219
216 U	MDSeq 262 216 U F	agccaataaccactcaggga	198	MDSeq 262 216 U R	taccttcaccagagggcagg	220
216 V	MDSeq 255 216 V F	cccatgggtgaattaccata	199	MDSeq 255 216 V R	ggcagaagactagtgctctg	221
216 V	MDSeq 256 216 V F	gctctgtgtgactctctac	200	MDSeq 256 216 V R	gcaggcagcttggaaattt	222
216 V	MDSeq 257 216 V F	actcagtcgaaccatagggc	201	MDSeq 257 216 V R	tatcatggagaccagatgic	223
216 V	MDSeq 258 216 V F	tgtgtgaccttgtctctgg	202	MDSeq 258 216 V R	gaccttgatccaagcctcc	224

216 V	MDSeq 358	216 V F	gcataagcaatggagaat	203	MDSeq 358	216 V R	atgttggtatagcgtgtg	225
216 V	MDSeq 365	216 V F	actcagtcgaaccataggc	204	MDSeq 365	216 V R	ttaatcatggagaccagatgc	226
216 Q	MDSeq 244	216 Q F	ggaggaagggttatgtgct	205	MDSeq 244	216 Q R	ctgaatggaggagcagaag	227
216 Q	MDSeq 292	216 Q F	gcaggaaggttcatgtct	206	MDSeq 292	216 Q R	ctgaatggaggagcagaag	228
216 KL	MDSeq 389	216 KL F	ggcatctggagaggaag	207	MDSeq 389	216 KL R	ccatgagatcgccacag	229
216 AA	MDSeq 360	216 AA F	tcgtccaccagattcaagt	208	MDSeq 360	216 AA R	atttcaaggtctgaatgagg	230
216 RS	MDSeq 300	216 RS F	agaaatgcctccaggagctt	209	MDSeq 300	216 RS R	actcttccatggccctctg	231
216 ST	MDSeq 301	216 ST F	gtgtgtctaccgactccag	210	MDSeq 301	216 ST R	accaccagggtcacagagaa	232
216 ST	MDSeq 303	216 ST F	ctgtctctctgagcctactcc	211	MDSeq 303	216 ST R	tcccaagaccaggctatgtc	233
216 ST	MDSeq 321	216 ST F	aacagagggtccagtgcc	212	MDSeq 321	216 ST R	ctggggatgagaagcagc	234
216 ST	MDSeq 322	216 ST F	agcgagttgttgatgggt	213	MDSeq 322	216 ST R	ctctcccttccctccac	235
216 ST	MDSeq 361	216 ST F	tgtcaggctgaagatagc	214	MDSeq 361	216 ST R	atttgtcagagggaagtgc	236
216 ST	MDSeq 362	216 ST F	gcacattctctgcacaat	215	MDSeq 362	216 ST R	caatttccctcaggctctgac	237
216 TU	MDSeq 339	216 TU F	ctgagcccgagaacctgtatt	216	MDSeq 339	216 TU R	tcagagcctggagggaatgt	238
216 UV	MDSeq 302	216 UV F	gtgagtgaggcaccagg	217	MDSeq 302	216 UV R	gttccgtgagtggtgggt	239
216 QR	MDSeq 359	216 QR F	ccatagtgccagggaagta	218	MDSeq 359	216 QR R	ctgggaggtcggtagcaaca	240

TABLE 10

SNP	Exon	PMP site	Location	Position	Sequence (20nt+allele+20nt)	SEQ ID	Allele	AA
1	A	-2	intron	4610	caagaaccttccagcgggtttctctccctctctcaggagtag -----a-----	242 373	c a	
2	A	-1	intron	4653	gccctctgagaccgacgggagggagcggtcggcggtca -----t-----	241 374	a t	
3	C	-2	intron	9826	ccaccatctcagctccacactctttttgcccaggctcga -----a-----	244 375	t a	
4	C	-1	intron	9827	caccatctcagctccacactctttttgcccaggctcga -----t-----	243 376	c t	
5	D	-2	intron	11661	tgggtcttcccatattcacatctccacaaactaagcatca -----g-----	246 377	t c	
6	D	-1	intron	11687	acaactaagccatcaccaaggctctctcttagccccaag -----c-----	245 378	g c	
7	D	1	exon	11912	caggatacatgaaacccactacgcccagatgggcagcca -----c-----	247 379	t c	Tyr His
8	F	1	exon	12411	agctgctacctggaaggaacctgtggccacaggatctct -----g-----	249 380	a g	Thr Ala
9	F	+1	intron	12545	ccctccaaatcagaagagacagggaattcacaggcctcaggt -----g-----	248 381	a g	
10	G	-1	intron	12637	acttcttctgggagctgggggttgggggtcagggtcacaagc -----a-----	250 382	g a	
11	I	1	exon	13197	tctctgcagtgggcgccggggctgtggcgacggcgcccca -----a-----	251 383	g a	
12	KL	+1	intron	13859	tggcgagggttactcctacacggggagagacacgctcgggtc -----t-----	286 384	c t	
13	KL	+2	intron	13921	ggctgctcactatggggcgcatcgtccctctccgctt -----t-----	287 385	g t	
14	KL	+3	intron	13938	gcgcgatgctccctgtcccgcttgggtgtgactttgcgc -----a-----	288 386	g a	

15	L	-2	intron	13988	ccctctctgggctctgcgctctggcggctgtagccaagc -----a-----	254 387	g a
16	L	-1	intron	14043	cagagaagcgcggggttgggggactgtccctccatgcacca -----a-----	253 388	g a
17	L	1	exon	14135	cagcgcgcgcagctgcgcgctctctccccaagggggcg -----l-----	255 389	c t
18	M	+1	intron	14481	ggttcagggtgaggggttcggggagcttgggagccggcctg -----l-----	252 390	g t
19	Q	-1	intron	15423	gtgagctctgcacacccgcacctctcttgcggtttgaatcc -----l-----	285 391	c t
20	S	1	exon	15865	tgctggccatgctctcctcaggtcctgctgctctctgtcccca -----a-----	257 392	g a
21	S	2	exon	15888	ctgctgcctctgctctccacagggcgcgcctggcctggtgtg -----c-----	258 393	g c
22	ST	+1	intron	16133	gaagttagcttgaacaggaggttccagtgcctccccagtcac -----l-----	259 394	g t
23	S	+1	intron	16158	agtggcctcccagtcacgcgagggggtggatccctgcccaca -----l-----	256 395	a t
24	ST	+3	intron	16361	gcctctgtctcaccagtttttgcggccctttgccacttcctct -----l-----	260 396	c t
25	ST	+4	intron	16404	acaaatcacctctgtcacccctctgaagtcccaaatgctg -----a-----	261 397	c a
26	ST	+5	intron	16465	tcacatcacactgggtcagctggggtgctggctgcccctgtgc -----l-----	262 398	c t
27	ST	+6	intron	16486	gggtgtggtgcctccctgtgcaggggcctcccttaaccacag -----l-----	263 399	c t
28	ST	+7	intron	16936	ggaaatgacaagggccttgggggatgggagtgggacagtcac -----a-----	264 400	g a
29	T	1	exon	17403	cctggcgcgcgttcaccacatgggaggttggggcccccacagcca -----c-----	267 401	t c
							Met Thr

30	T	2	exon	17432	gcccacagccactggacagccctggccctgggtgagtga -----t-----	268 402	c t	Pro Ser
31	TU	-1	intron	17451	gccctggccctgggtgagtgagcaccagggggaggtgga -----t-----	269 403	g t	
32	T	+1	intron	17510	agggctcatgctcctcctcccttcagatgggcacaccc -----t-----	265 404	c t	
33	T	+2	intron	17571	gcccctcccagcccccagggtcctcctgctgaccattcac -----g-----	266 405	t g	
34	V	-4	intron	17834	atgacctcttggttatcatgagacacaggatgctggaacc -----g-----	273 406	g c	
35	V	-3	intron	17916	ctggctcctcaactgagtggagatgggctctctgccacacagc -----g-----	272 407	a g	
36	V	-2	intron	17924	cactgagt-gaggatgggctctctgccacacagcttgacgcc -----c-----	271 408	t c	
37	V	-1	intron	17958	tgcagcctggggcccccagtccttaggggacacacatatcctc -----a-----	270 409	c a	
38	V	1	exon	17997	tcctcatctcagcagatcaagtcaggtccagatgccaatcctg -----t-----	281 410	a t	Gln His
39	V	2	exon	18174	ttcttccccagatggagcttcgacccaccactccaggaac -----t-----	280 411	c t	
40	V	3	exon	18206	tcaggaaacccagagccacattagaagttcctgagggctgg -----c-----	279 412	t c	
41	V	4	exon	18476	actgagtcacactccctcctgcagcctggctggcctctgcaa -----g-----	278 413	c g	
42	V	5	3' UTR	18497	agcctggctggcctctgcaacacacataaattttggggacc -----g-----	277 414	a g	
43	V	6	3' UTR	18760	atcccagcactttgggaagcggggtaggaggatcaccaga -----t-----	276 415	c t	
44	V	7	exon	18787	ggaggatcacagagccagcaggtccacacacagcctgggc -----g-----	275 416	c g	



45	V	8	3' UTR	18833	agcaagacacgcgcatctacagaaaaattttaaaatagctg -----g-----	274 417	g a
46	V	+2	intron	19094	ctgaggaccacacggggcggtgggtggcggtg -----g-----	282 418	t c
47	V	+4	intron	19160	ggctggcaggcgagcctagatggcagccagagcccccaggc -----g-----	283 419	a g
48	V	+5	intron	19244	ctttgctctgtcaactcctgcctccctggcggttcacattc -----t-----	284 420	c t

Gene 216 SNP Name Conversion Chart					
Former SNP Name	Present SNP Name	Former SNP Name	Present SNP Name		
216 T 2	216 V 7	216 Q +1	216 S +1		
216 T 3	216 V 6	216 Q 2	216 S 2		
216 T 4	216 V 5	216 Q 1	216 S 1		
216 T 5	216 V 4	216 U -1	216 Q -1		
216 T 6	216 V 3	216 L +1	216 M +1		
216 T 7	216 V 2	216 L 1	216 L 1		
216 T 8	216 V 1	216 L -1	216 L -1		
216 T +1	216 V -1	216 L -2	216 L -2		
216 T +2	216 V -2	216 V +2	216 KL +2		
216 T +3	216 V -3	216 V +1	216 KL +1		
216 T +4	216 V -4	216 L 1	216 L 1		
216 R +2	216 T +2	216 G -1	216 G -1		
216 R +1	216 T +1	216 F +1	216 F +1		
216 R 2	216 T 2	216 F 1	216 F 1		
216 R 1	216 T 1	216 D 1	216 D 1		
216 QR +7	216 ST +7	216 D -1	216 D -1		
216 QR +6	216 ST +6	216 D -2	216 D -2		
216 QR +5	216 ST +5	216 A -1	216 A -1		
216 QR +4	216 ST +4	216 T 1	216 V 8		

Using an in-house program called snp\_view; the genomic structure of the gene was diagrammed (Figure 11). In Figure 11, the exons are shown to scale and the SNPs are identified by their location along the genomic BAC DNA. The polymorphic sites identified in the Gene 216 genomic sequence are also shown by the underlined nucleotides in Figure 29. The polymorphic sites discovered within the cDNA and the corresponding amino acid position in Gene 216 are underlined in Figure 24. It will be understood by those of skill in the art that the SNPs identified in the Gene 216 genomic sequence can be correlated to the SNP positions identified in the Gene 216 cDNA sequence by aligning the genomic and cDNA sequences.

#### **EXAMPLE 11: Polymorphism Genotyping**

Putative variants were confirmed by sequencing. Following this, rapid allele specific assays were designed to type more than 400 individuals (> 200 cases and > 200 controls). These assays were used in the association studies. All coding SNPs (cSNPs) that resulted in an amino acid change (ccSNPs) were typed. Neutral polymorphisms were typed if: 1) the polymorphism was identified in an exon which lacked a ccSNP; 2) the polymorphism was identified in an exon which contained a ccSNP, but the two polymorphisms showed different frequencies; and 3) the polymorphism was identified in an intronic region adjacent to an exon which lacked a cSNP. If results from the association studies appeared positive, additional neutral polymorphisms were typed. More than 30 allele specific assays from Gene 216 were typed for the case control population (Table 11).

Two types of allele specific assays (ASAs) were used. If the SNP resulted in a mutation that created or abolished a restriction site, restriction fragment length polymorphisms (RFLPs) were obtained from PCR products that spanned the variants. The RFLPs were then analyzed. If the polymorphisms did not result in RFLPs, allele specific oligonucleotide assays were used. For these assays, PCR products that spanned the polymorphism were electrophoresed on agarose gels and transferred to nylon membranes by

Southern blotting. Oligomers 16-20 bp in length were designed such that the middle base was specific for each variant. The oligomers were labeled and successively hybridized to the membrane in order to determine genotypes. The specific method used to type each SNP is indicated in Table 11.

5           Table 11 below contains the information relating to the specific assay used. Column 1 lists the SNP designation number. Column 2 lists the specific assay used, either RFLP or ASO. Column 3 lists the enzyme used in the RFLP assay (described below). Columns 4 and 6 list the sequence of the primers used in the ASO assay (described below). Columns 5 and 7 list the  
10           corresponding SEQ ID NOS for the primers.

1.       RFLP Assay: The amplicon containing the polymorphism was PCR amplified using primers that were used to generate a fragment for sequencing (sequencing primers) or SSCP (SSCP primers). The appropriate population of individuals was PCR amplified in 96 well microtiter plates.

15           Enzymes were purchased from NEB. The restriction cocktail containing the appropriate enzyme for the particular polymorphism is added to the PCR product. The reaction was incubated at the appropriate temperature according to the manufacturer's recommendations (NEB) for 2-3 hr, followed by a 4°C incubation. After digestion, the digestion products were size fractionated using  
20           the appropriate agarose gel depending on the assay specifications (2.5%, 3%, or Metaphor, FMC Bioproducts). Gels were electrophoresed in 1 X TBE Buffer at 170 Volts for approximately 2 hr. The gel was illuminated using ultraviolet light and the image was saved as a Kodak 1D file. Using the Kodak 1D image analysis software, the images were scored and the data was exported to  
25           Microsoft EXCEL (Microsoft, Redmond, WA).

2.       ASO assay: The amplicon containing the polymorphism was PCR amplified using primers that were used to generate a fragment for sequencing (sequencing primers) or SSCP (SSCP primers). The appropriate population from individuals was PCR amplified in 96-well microtiter plates and  
30           re-arrayed into 384-well microtiter plates using a Tecan Genesis RSP200. The amplified products were loaded onto 2% agarose gels and size fractionated at

150 V for 5 min. The DNA was transferred from the gel to Hybond N+ nylon membrane (Amersham-Pharmacia) using a Vacuum blotter (Bio-Rad). The filter containing the blotted PCR products was transferred to a dish containing 300 ml pre-hybridization solution. This solution contained 5 X SSPE (pH 7.4), 2% SDS, and 5 X Denhardt's. The filter was incubated in pre-hybridization solution at 40°C for over 1 hr. After pre-hybridization, 10 ml of the pre-hybridization solution and the filter were transferred to a washed glass bottle.

For these assays, the allele specific oligonucleotides (ASO) were designed with the polymorphism in the middle. The size of the oligonucleotide was dependent upon the GC content of the sequence around the polymorphism. Those ASOs that had a G or C polymorphism were designed so that the  $T_m$  was between 54-56°C and those that had an A or T variance were designed so that the  $T_m$  was between 60-64°C. All oligonucleotides were phosphate free at the 5' end and purchased from GibcoBRL. For each polymorphism, 2 ASOs were designed: one for each variant.

The two ASOs that represented the polymorphism were resuspended at a concentration of 1 µg/µl. Each ASO was end-labeled separately with  $\gamma$ -ATP<sup>32</sup> (6000 Ci/mmol) (NEN) using T4 polynucleotide kinase according to manufacturer recommendations (NEB). The end-labeled products were removed from the unincorporated  $\gamma$ -ATP<sup>32</sup> by passing the reactions through Sephadex G-25 columns according to manufacturers recommendation (Amersham-Pharmacia). The entire end-labeled product of one ASO was added to the bottle containing the appropriate filter and 10 ml hybridization solution. Hybridization solution included 5 X SSPE (pH 7.4), 2% SDS, and 5 X Denhardt's solution. The hybridization reaction was placed in a rotisserie oven (Hybaid, Franklin, MA) and left at 40°C for a minimum of 4 hr. The other ASO was stored at -20°C.

After the prerequisite hybridization time had elapsed, the filter was removed from the bottle and transferred to 1 L of wash solution pre-warmed to 45°C. Wash solution contained 0.1 X SSPE (pH 7.4) and 0.1% SDS. After 15 min, the filter was transferred to another L of wash solution pre-warmed to

50°C. After 15 min, the filter was wrapped in Saran, placed in an autoradiograph cassette and an X-ray film (Kodak) placed on top of the filter. Typically, an image would be observed on the film within 1 hr. After an image had been captured on film for the 50°C wash, the process was repeated for 5 wash steps at 55°C, 60°C and 65°C. The image that captured the best result was used.

The ASO was removed from the filter by adding 1 L of boiling strip solution. This solution contained 0.1 x SSPE (pH 7.4) and 0.1% SDS. This was repeated two more times. After removing the ASO the filter was pre-10 hybridized in 300 ml pre-hybridization solution at 40°C for over 1 hr. Prehybridization solution contained 5 X SSPE (pH 7.4), 2% SDS, and 5 X Denhardt's. The second end-labeled ASO corresponding to the other variant was removed from storage at -20°C and thawed at room temperature. The filter was placed into a glass bottle along with 10 ml hybridization solution and the entire end-labeled product of the second ASO. Hybridization solution 15 included 5 X SSPE (pH 7.4), 2% SDS, and 5 X Denhardt's solution. The hybridization reaction was placed in a rotisserie oven (Hybaid) and left at 40°C for a minimum of 4 hr. After the hybridization, the filter was washed at various temperatures and images captured on film as described above.

20 The two films that best captured the allele-specific assay with the two ASOs were converted into digital images by scanning them into Adobe PhotoShop (Adobe, San Jose, CA). These images were overlaid against each other in Graphic Converter and then scored.

TABLE 11

SNP	SNP name	ASA Type	RFLP Enzyme	ASO Primer1	SEQ ID NO:	ASO Primer2	SEQ ID NO:
1	A -2	ASO		ctctctctcttggcgac	290	tcctctctatftggcgccc	300
2	A -1	ASO		ggcgctccaccocgctcg	289	ggcgctccctcccgctcg	299
3	C -2	ASO		gctccacactcttcttgcc	292	gctccacactcttcttgcc	302
4	C -1	ASO		tcacacactcttcttgcc	291	ctccacactcttcttgccca	301
5	D -2	Alt. Meth					
6	D -1	ASO		tcaccaagggctctctctct.	293	tcaccaagcctctctctct	303
7	D 1	RFLP	XcmI				
8	F 1	ASO		tggaaagggaacctgggcc	295	tggaaaggagacgctgagg	305
9	F +1	ASO		cagaagcgacaggaattcaca	294	agaagagacaggggaattcac	304
10	G -1	ASO		agctggggttgggggt	367	ggagctggggaattgggggt	370
11	I 1	ASO		gccgggggctctgggg	368	cgccgggggacgtggggc	371
12	KL +1	RFLP	BsrI				
13	KL +2	RFLP	Eco109 I				
14	KL +3	ASO					
15	L -2	ASO		ctctgcgcgtctggcg	298	gctctgcgcactctggcgg	308
16	L -1	ASO		gggttggggagctgtc	297	ggggttggaggagactgtcc	307
17	L 1	RFLP	Bss/HI				
18	M +1	ASO		gggtttcgggggagcttg	296	agggtttctgtggagcttgg	306
19	Q -1	RFLP	HinfI				
20	S 1	ASO		ctctcaggtctctgtcg	310	ctctctcagcatctctgtcgc	323
21	S 2	RFLP	KasI				
22	ST <sub>L</sub> +1	ASO		aacagaggtttccagtg	311	gaacagaggtttccagtgcc	324
23	S +1	ASO		agtcaggcgagggggttg	309	agtcaggcggtgggggttg	322
24	ST +3	ASO		accagtttctggcccttt	312	caccagtttctggccctttg	325
25	ST +4	ASO		cgtcaccccttgaagt	313	cgtcaccccttgaagttc	326
26	ST +5	ASO		tcagctcgggtctgg	314	gggtcagctgtgggtctgg	327
27	ST <sub>L</sub> +6	RFLP	BsNI				
28	ST <sub>L</sub> +7	ASO		ggcttgggggatgga	315	agggcttgggggatgggat	328

29	T 1	RFLP	NcoI				
30	T 2	ASO		actgagagacctggc	317	actgagagctctggc	330
31	TU -1	ASO		tggcgctctactcacc	369	ccgggctctaaactcaccca	372
32	T +1	ASO		tctctgcctctctccag	316	tctctgcctctctccag	329
33	T +2	RFLP	BglI				
34	V -4	RFLP	BsaI				
35	V -3	Alt. Meth					
36	V -2	ASO		ctgtgtggcagagagccca	318	tgtggcaggaggagccca	331
37	V -1	RFLP	Bsu36I				
38	V 1	RFLP	NlaIII				
39	V 2	RFLP	TaqI				
40	V 3	ASO		gaactctagtgtggctct	320	ggaaactctaatgtggctctg	333
41	V 4	RFLP	Fnu4HI				
42	V 5	ASO		aattatgtttgttcagaggc	319	attatgtttctgcagagg	332
43	V 6	RFLP	MspI				
44	V 7	RFLP	Cac8I				
45	V 8	Alt. Meth					
46	V +2	ASO					
47	V +4	RFLP	StyI				
48	V +5	ASO		ccaaggaggcaggaggt	321	ccaaggaggacagagctga	334

**EXAMPLE 12: Association Study Analysis**

1. Case-Control Study: In order to determine whether polymorphisms in candidate genes were associated with the asthma phenotype, association studies were performed using a case-control study design. For a well-matched design, the case-control approach is more powerful than the family based transmission disequilibrium test (TDT) (N.E. Morton and A. Collins, 1998, *Proc. Natl. Acad. Sci. USA* **95**:11389-93). Case-control studies are, however, sensitive to population heterogeneity.

To avoid issues of population admixture, which can bias case-control studies, the unaffected controls were collected in both the US and the UK. A total of three hundred controls were collected, 200 in the UK and 100 in the US. Inclusion into the study required that the control individual was negative for asthma, as determined by self-report of never having asthma, had no first-degree relatives with asthma, and was negative for eczema and symptoms indicative of atopy within the past 12 months. Data from an abbreviated questionnaire similar to that administered to the affected sib pair families were collected. Results from skin prick tests to 4 common aeroallergens (house dust mite, cat, grass, and tree) were also collected. The results of the skin prick test were used to select a subset of controls that were most likely to be asthma and atopy negative.

A subset of unrelated cases was selected from the affected sib pair families based on the evidence for linkage at chromosomal locations flanking a given gene. One affected sib demonstrating identity-by-descent (IBD) at the appropriate marker loci was selected from each family. Since the appropriate cases could have varied for each gene in the chromosome 20 region, a larger collection of individuals who were IBD across a larger interval were genotyped. A subset of these individuals was used in the analyses. On average, 130 IBD affected individuals and 200 controls were compared for allele and genotype frequencies. This number provided an 80% power to detect a difference of 5% or greater between the two groups for a rare allele ( $\leq 5\%$ ) at a 0.05 level of significance. For a common allele (50%), the number provided an 80% power



to detect a difference of 10% or more between the two groups.

For each polymorphism, the frequency of the alleles in the control and case populations was compared using a Fisher exact test. A mutation that increased susceptibility to the disease was predicted to be more prevalent in the cases than in the controls, while a protective mutation was predicted to be more prevalent in the control group. Similarly, the genotype frequencies of the SNPs were compared between cases and controls. P-values for both the allele and genotype were plotted against a coordinate system based on genomic sequence to visualize regions where allelic association was present. A small p-value (or a large value of  $-\log(p)$ , as plotted in the figures described below) was indicative of an association between the SNPs and the disease phenotype. The analysis was repeated for the US and UK population separately to adjust for the possibility of genetic heterogeneity.

2. Association test with individual SNPs: Chromosomal regions harboring asthma susceptibility genes were identified by association studies using the SNP typing data. Two separate phenotypes were used in these analyses: asthma and bronchial hyper-responsiveness.

a. Asthma Phenotype: The significance levels (p-values) for allelic association of all typed SNPs in Gene 216 to the asthma phenotype are plotted in Figure 25 (combined population) and Figure 26 (US and UK populations, separately). The most significant result in the combined population was observed for Gene 216 exon SNP V -1. For this SNP, 92.4% of the cases were carriers of the C allele, whereas the C allele was observed in only 85.2% of the controls ( $p = 0.0055$ ). Five additional SNPs in Gene 216 (V4, ST+7, ST+4, S1, and Q-1) were significant at the 0.05 level. Frequencies of the allele seen more often in the cases than in the controls and p-values for the association with the asthma phenotype in Gene 216 are presented in Tables 12, 13, and 14 for the combined population and for the UK and US populations, separately.

**TABLE 12**

Asthma Yes/No Combined US and UK							
SNP	ALLELE	FREQUENCIES				P-VALUE	GENOTYPE P-VALUE
		CNTL	N	CASE	N		
A-1	T	2.4%	212	2.7%	130	0.8039	0.8016
D-2	T	0.7%	214	0.8%	127	1.0000	1.0000
D-1	C	62.4%	205	65.7%	118	0.4449	0.5390
D1	C	0.0%	215	0.4%	131	0.3786	0.3786
F1	A	96.8%	217	96.9%	129	1.0000	1.0000
F+1	G	65.2%	197	70.4%	120	0.1913	0.4109
G-1	T	90.7%	210	91.3%	127	0.8900	0.7683
I1	G	84.9%	212	85.3%	129	0.9124	1.0000
KL+1	G	96.1%	217	97.2%	125	0.5223	0.5145
KL+2	C	71.3%	216	77.1%	129	0.1085	0.2262
L-2	G	92.9%	212	93.1%	131	1.0000	0.9379
L-1	A	11.1%	212	11.2%	130	1.0000	1.0000
L1	C	99.3%	217	99.6%	131	1.0000	1.0000
M+1	G	88.7%	213	88.9%	131	1.0000	0.9672
Q-1	C	85.0%	217	91.2%	131	<b>0.0184</b>	0.0659
S1	G	89.5%	209	94.6%	130	<b>0.0233</b>	0.0717
S2	G	73.7%	217	80.0%	130	0.0662	0.0834
S+1	A	51.2%	206	52.5%	120	0.8075	0.6608
ST+4	A	51.5%	205	60.1%	129	<b>0.0313</b>	0.1043
ST+5	T	46.4%	210	48.8%	129	0.5794	0.4165
ST+6	T	0.5%	216	0.8%	129	0.6323	0.6317
ST+7	G	78.1%	215	85.8%	130	<b>0.0160</b>	<b>0.0248</b>
T1	C	11.3%	217	11.8%	131	0.9025	0.7483
T2	T	9.4%	208	10.8%	125	0.5928	0.7656
T+1	C	88.7%	191	88.8%	120	1.0000	0.8394
T+2	T	88.3%	217	88.9%	131	0.8076	0.9005
V-4	G	24.4%	215	26.9%	130	0.4713	0.6808
V-3	A	37.1%	209	38.8%	129	0.6834	0.6613
V-2	T	36.8%	212	38.1%	130	0.7451	0.7909
V-1	C	85.2%	216	92.4%	131	<b>0.0055</b>	<b>0.0178</b>
V1	A	96.5%	211	98.1%	130	0.2515	0.2443
V2	C	96.3%	215	98.5%	129	0.1576	0.1513
V3	T	77.8%	214	78.4%	125	0.9235	0.9791
V4	C	76.7%	217	83.6%	131	<b>0.0336</b>	<b>0.0370</b>
V5	A	96.3%	215	98.5%	129	0.1576	0.1513
V6	T	8.7%	213	9.5%	131	0.7841	0.6895
V7	C	66.5%	215	71.5%	128	0.2029	0.1482

**TABLE 13**

Asthma Yes/No UK population							
SNP	ALLELE	FREQUENCIES				ALLELE P-VALUE	GENOTYPE P-VALUE
		CNTL	N	CASE	N		
A-1	T	1.1%	135	3.4%	104	0.1110	0.1075
D-2	T	0.7%	139	1.0%	101	1.0000	1.0000
D-1	C	61.1%	135	65.5%	97	0.3807	0.2619
D1	C	0.0%	139	0.5%	104	0.4280	0.4280
F1	A	97.9%	140	98.0%	102	1.0000	1.0000
F+1	G	64.1%	128	74.2%	93	<b>0.0295</b>	0.0711
G-1	C	9.8%	137	9.9%	101	1.0000	0.4913
I1	G	83.7%	138	89.2%	102	0.1094	0.1323
KL+1	G	97.1%	140	98.0%	99	0.7685	0.7655
KL+2	C	71.6%	139	79.1%	103	0.0717	0.1519
L-2	A	7.3%	137	7.7%	104	0.8633	1.0000
L-1	G	87.2%	137	91.8%	103	0.1380	0.3380
L1	C	99.3%	140	99.5%	104	1.0000	1.0000
M+1	G	87.0%	138	91.8%	104	0.1059	0.2969
Q-1	C	86.1%	140	92.3%	104	<b>0.0419</b>	0.0763
S1	G	89.4%	132	95.2%	104	<b>0.0260</b>	0.0567
S2	G	72.9%	140	84.0%	103	<b>0.0041</b>	<b>0.0128</b>
S+1	T	46.9%	129	49.5%	97	0.6346	0.5458
ST+4	A	48.1%	128	59.2%	103	<b>0.0191</b>	0.0718
ST+5	T	44.4%	133	50.0%	102	0.2273	0.2470
ST+6	T	0.0%	139	1.0%	103	0.1806	0.1801
ST+7	G	79.5%	139	86.4%	103	0.0535	0.1362
T1	T	86.8%	140	91.4%	104	0.1473	0.3472
T2	C	89.6%	134	91.8%	98	0.4279	0.7007
T+1	C	86.9%	122	91.1%	95	0.2211	0.4281
T+2	T	87.5%	140	87.5%	104	1.0000	1.0000
V-4	G	25.2%	139	26.7%	103	0.7529	0.6628
V-3	A	38.1%	134	40.2%	102	0.7032	0.8627
V-2	T	37.6%	137	39.3%	103	0.7055	0.9223
V-1	C	86.4%	140	93.8%	104	<b>0.0105</b>	<b>0.0243</b>
V1	A	97.8%	137	98.5%	103	0.7385	0.7359
V2	C	97.5%	138	99.0%	102	0.3129	0.3082
V3	T	78.5%	137	80.1%	98	0.7301	0.8875
V4	C	75.4%	140	83.7%	104	<b>0.0328</b>	<b>0.0288</b>
V5	A	97.1%	140	98.5%	103	0.3689	0.3633
V6	T	8.3%	139	9.6%	104	0.6308	0.7329
V7	C	65.8%	139	74.3%	101	0.0566	0.1266

**TABLE 14**

Asthma Yes/No US population							
SNP	ALLELE	FREQUENCIES				ALLELE P-VALUE	GENOTYPE P-VALUE
		CNTL	N	CASE	N		
A-1	A	95.5%	77	100.0%	26	0.1953	0.1872
D-2	C	99.3%	75	100.0%	26	1.0000	1.0000
D-1	C	65.0%	70	66.7%	21	1.0000	0.7300
D1	T	100.0%	76	100.0%	27	1.0000	1.0000
F1	G	5.2%	77	7.4%	27	0.5136	0.5043
F+1	A	32.6%	69	42.6%	27	0.2401	0.3270
G-1	T	91.8%	73	96.2%	26	0.3635	0.3440
I1	A	12.8%	74	29.6%	27	<b>0.0105</b>	<b>0.0074</b>
KL+1	G	94.2%	77	94.2%	26	1.0000	1.0000
KL+2	A	29.2%	77	30.8%	26	0.8614	0.8889
L-2	G	93.3%	75	96.3%	27	0.7362	0.5089
L-1	A	8.0%	75	22.2%	27	<b>0.0116</b>	<b>0.0123</b>
L1	C	99.4%	77	100.0%	27	1.0000	1.0000
M+1	T	8.0%	75	22.2%	27	<b>0.0116</b>	<b>0.0123</b>
Q-1	C	83.1%	77	87.0%	27	0.6654	0.8280
S1	G	89.6%	77	92.3%	26	0.7873	1.0000
S2	C	24.7%	77	35.2%	27	0.1571	0.1404
S+1	A	48.1%	77	60.9%	23	0.1345	0.3169
ST+4	A	57.1%	77	63.5%	26	0.5150	0.5127
ST+5	C	50.0%	77	55.6%	27	0.5287	0.6337
ST+6	C	98.7%	77	100.0%	26	1.0000	1.0000
ST+7	G	75.7%	76	83.3%	27	0.3413	0.0732
T1	C	7.8%	77	24.1%	27	<b>0.0030</b>	<b>0.0055</b>
T2	T	7.4%	74	20.4%	27	<b>0.0188</b>	<b>0.0208</b>
T+1	T	8.0%	69	20.0%	25	<b>0.0334</b>	<b>0.0361</b>
T+2	T	89.6%	77	94.4%	27	0.4127	0.3874
V-4	G	23.0%	76	27.8%	27	0.5795	0.6743
V-3	G	64.7%	75	66.7%	27	0.8684	0.4960
V-2	C	64.7%	75	66.7%	27	0.8684	0.4960
V-1	C	82.9%	76	87.0%	27	0.5262	0.8281
V1	A	93.9%	74	96.3%	27	0.7308	0.7226
V2	C	94.2%	77	96.3%	27	0.7320	0.7241
V3	C	23.4%	77	27.8%	27	0.5819	0.6932
V4	C	79.2%	77	83.3%	27	0.5583	0.7765
V5	A	94.7%	75	98.1%	26	0.4519	0.4404
V6	C	90.5%	74	90.7%	27	1.0000	1.0000
V7	G	32.2%	76	38.9%	27	0.4053	0.1776

b. Bronchial Hyper-responsiveness: The analyses were repeated using asthmatic children with borderline to severe BHR ( $PC_{20} \leq 16$  mg/ml) or  $PC_{20}(16)$ , as described in the linkage section. First, sibling pairs were identified where both sibs were affected and satisfied this new criterion. Of these pairs, one sib was included in the case/control analyses if they showed evidence of linkage at the gene of interest. This phenotype was more restrictive than the Asthma yes/no criteria. Hence, the number of cases included in the analyses was reduced approximately in half. If the  $PC_{20}(16)$  subgroup represented a more genetically homogeneous sample, it was expected that an increase in the effect size compared to the one observed in the original set of cases would be observed. It was also possible that the reduction in sample size would produce estimates that were less accurate. Such estimates could obscure a trend in allele frequencies in the control group, the original set of cases, and the  $PC_{20}(16)$  subgroup. In addition, it was possible that the reduction in sample size would induce a reduction in power (and increase in p values) in spite of the larger effect size.

The significance levels (p-values) for allelic association of all typed SNPs in Gene 216 to the BHR phenotype are plotted in Figure 27 (combined population) and Figure 28 (US and UK populations, separately). Frequencies of the alleles seen more often in the cases than in the controls and p-values for the association with the BHR phenotype in Gene 216 are presented in Tables 15, 16, and 17 for the combined population and for the UK and US populations, separately. As before, multiple SNPs in Gene 216 were associated with the phenotype in each separate population. In the UK population, the most significant SNP was in Gene 216, exon S2. For this SNP, 87% of the cases were carriers of the G allele compared to 72.9% for the controls ( $p = 0.0038$ ). For the US population, the most significant association was found with the SNP in Gene 216 exon T 1, where 28.6% of the cases carried the C allele compared to 7.8% for the controls ( $p = 0.0041$ ).

In summary, Gene 216 was associated with the phenotypes of both

- asthma and bronchial hyper-responsiveness. Association was found with multiple SNPs in both the UK and US populations. The 3' region of the gene, which contains the transmembrane domain, the cytoplasmic domain, and the 3' UTR, appeared to have the strongest association. Taken together, these
- 5 data strongly suggested that Gene 216 was an asthma susceptibility gene.

**TABLE 15**

BHR Combined US and UK							
SNP	ALLELE	FREQUENCIES				ALLELE P-VALUE	GENOTYPE P-VALUE
		CNTL	N	CASE	N		
A-1	A	97.6%	212	97.7%	64	1.0000	1.0000
D-2	T	0.7%	214	0.8%	63	1.0000	1.0000
D-1	G	37.6%	205	38.3%	60	0.9149	0.7497
D1	C	0.0%	215	0.8%	64	0.2294	0.2294
F1	A	96.8%	217	97.6%	62	0.7752	0.7715
F+1	G	65.2%	197	66.7%	57	0.8234	0.3665
G-1	C	9.3%	210	9.5%	63	1.0000	0.9355
I1	G	84.9%	212	86.7%	64	0.6709	0.8958
KL+1	G	96.1%	217	97.6%	63	0.5874	0.5802
KL+2	C	71.3%	216	75.0%	64	0.4343	0.7291
L-2	A	7.1%	212	8.6%	64	0.5661	0.5313
L-1	G	88.9%	212	89.7%	63	0.8722	1.0000
L1	T	0.7%	217	0.8%	64	1.0000	1.0000
M+1	G	88.7%	213	89.8%	64	0.8722	0.9410
Q-1	C	85.0%	217	89.8%	64	0.1915	0.5304
S1	G	89.5%	209	93.7%	63	0.2251	0.5211
S2	G	73.7%	217	79.7%	64	0.2009	0.0664
S+1	A	51.2%	206	51.8%	57	1.0000	0.7632
ST+4	A	51.5%	205	58.9%	62	0.1521	0.3393
ST+5	T	46.4%	210	46.8%	63	1.0000	0.5530
ST+6	C	99.5%	216	100.0%	63	1.0000	1.0000
ST+7	G	78.1%	215	82.5%	63	0.3199	0.1216
T1	C	11.3%	217	11.7%	64	0.8750	0.7576
T2	C	90.6%	208	91.1%	62	1.0000	1.0000
T+1	C	88.7%	191	89.2%	60	1.0000	0.7540
T+2	T	88.3%	217	88.3%	64	1.0000	0.8975
V-4	G	24.4%	215	27.0%	63	0.5602	0.2603
V-3	A	37.1%	209	39.7%	63	0.6016	0.8755
V-2	T	36.8%	212	39.1%	64	0.6770	0.8930
V-1	C	85.2%	216	90.6%	64	0.1413	0.3117
V1	A	96.5%	211	97.6%	63	0.7758	0.7721
V2	C	96.3%	215	97.7%	64	0.5856	0.5786
V3	T	77.8%	214	78.3%	60	1.0000	0.8426
V4	C	76.7%	217	80.5%	64	0.4009	0.4077
V5	A	96.3%	215	98.4%	62	0.3878	0.3797
V6	T	8.7%	213	9.4%	64	0.8592	0.6092

V7	C	66.5%	215	67.7%	62	0.8294	0.1358
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**TABLE 16**

BHR UK population							
SNP	ALLELE	FREQUENCIES				ALLELE P-VALUE	GENOTYPE P-VALUE
		CNTL	N	CASE	N		
A-1	T	1.1%	135	3.0%	50	0.3500	0.3461
D-2	T	0.7%	139	1.0%	49	1.0000	1.0000
D-1	C	61.1%	135	61.5%	48	1.0000	0.5047
D1	C	0.0%	139	1.0%	50	0.2646	0.2646
F1	A	97.9%	140	97.9%	48	1.0000	1.0000
F+1	G	64.1%	128	73.3%	43	0.1466	0.2885
G-1	C	9.9%	137	10.2%	49	1.0000	0.9269
I1	G	83.7%	138	91.0%	50	0.0952	0.2406
KL+1	G	97.1%	140	98.0%	49	1.0000	1.0000
KL+2	C	71.6%	139	79.0%	50	0.1860	0.3615
L-2	A	7.3%	137	9.0%	50	0.6623	0.5686
L-1	G	87.2%	137	93.9%	49	0.0899	0.2787
L1	T	0.7%	140	1.0%	50	1.0000	1.0000
M+1	G	87.0%	138	94.0%	50	0.0638	0.2367
Q-1	C	86.1%	140	93.0%	50	0.0752	0.2087
S1	G	89.4%	132	96.0%	50	0.0603	0.1968
S2	G	72.9%	140	87.0%	50	<b>0.0038</b>	<b>0.0128</b>
S+1	T	46.9%	129	51.1%	45	0.5407	0.6988
ST+4	A	48.1%	128	57.1%	49	0.1538	0.2564
ST+5	T	44.4%	133	49.0%	49	0.4771	0.5020
ST+6	C	100.0%	139	100.0%	49	1.0000	1.0000
ST+7	G	79.5%	139	85.7%	49	0.2294	0.3049
T1	T	86.8%	140	93.0%	50	0.1041	0.3226
T2	C	89.6%	134	94.8%	48	0.1494	0.4752
T+1	C	86.9%	122	92.6%	47	0.1838	0.3875
T+2	G	12.5%	140	14.0%	50	0.7290	0.6834
V-4	G	25.2%	139	26.5%	49	0.7889	0.1160
V-3	A	38.1%	134	41.8%	49	0.5461	0.6617
V-2	T	37.6%	137	41.0%	50	0.5508	0.6328
V-1	C	86.4%	140	94.0%	50	<b>0.0454</b>	0.1307
V1	A	97.8%	137	98.0%	49	1.0000	1.0000
V2	C	97.5%	138	98.0%	50	1.0000	1.0000
V3	T	78.5%	137	79.4%	46	1.0000	0.9547
V4	C	75.4%	140	82.0%	50	0.2122	0.2778
V5	A	97.1%	140	98.0%	49	1.0000	1.0000
V6	T	8.3%	139	9.0%	50	0.8352	0.6515
V7	C	65.8%	139	74.0%	48	0.1635	0.1885

**TABLE 17**

BHR US population							
SNP	ALLELE	FREQUENCIES				ALLELE	GENOTYPE
		CNTL	N	CASE	N	P-VALUE	P-VALUE
A-1	A	95.5%	77	100.0%	14	0.5975	0.5899
D-2	C	99.3%	75	100.0%	14	1.0000	1.0000
D-1	G	35.0%	70	37.5%	12	0.8204	0.8258
D1	T	100.0%	76	100.0%	14	1.0000	1.0000
F1	A	94.8%	77	96.4%	14	1.0000	1.0000
F+1	A	32.6%	69	53.6%	14	0.0510	0.0665
G-1	T	91.8%	73	92.9%	14	1.0000	1.0000
I1	A	12.8%	74	28.6%	14	<b>0.0455</b>	<b>0.0463</b>
KL+1	G	94.2%	77	96.4%	14	1.0000	1.0000
KL+2	A	29.2%	77	39.3%	14	0.3730	0.2711
L-2	A	6.7%	75	7.1%	14	1.0000	1.0000
L-1	A	8.0%	75	25.0%	14	<b>0.0149</b>	<b>0.0227</b>
L1	C	99.4%	77	100.0%	14	1.0000	1.0000
M+1	T	8.0%	75	25.0%	14	<b>0.0149</b>	<b>0.0227</b>
Q-1	T	16.9%	77	21.4%	14	0.5910	0.6593
S1	A	10.4%	77	15.4%	13	0.4980	0.4470
S2	C	24.7%	77	46.4%	14	<b>0.0233</b>	<b>0.0331</b>
S+1	A	48.1%	77	62.5%	12	0.2724	0.4060
ST+4	A	57.1%	77	65.4%	13	0.5212	0.7976
ST+5	C	50.0%	77	60.7%	14	0.3130	0.4007
ST+6	C	98.7%	77	100.0%	14	1.0000	1.0000
ST+7	A	24.3%	76	28.6%	14	0.6391	0.2476
T1	C	7.8%	77	28.6%	14	<b>0.0041</b>	<b>0.0072</b>
T2	T	7.4%	74	21.4%	14	<b>0.0333</b>	<b>0.0469</b>
T+1	T	8.0%	69	23.1%	13	<b>0.0321</b>	<b>0.0452</b>
T+2	T	89.6%	77	96.4%	14	0.4778	0.4545
V-4	G	23.0%	76	28.6%	14	0.6296	0.7242
V-3	G	64.7%	75	67.9%	14	0.8311	1.0000
V-2	C	64.7%	75	67.9%	14	0.8311	1.0000
V-1	A	17.1%	76	21.4%	14	0.5937	0.6635
V1	A	93.9%	74	96.4%	14	1.0000	1.0000
V2	C	94.2%	77	96.4%	14	1.0000	1.0000
V3	C	23.4%	77	25.0%	14	0.8130	0.7738
V4	G	20.8%	77	25.0%	14	0.6206	0.6767
V5	A	94.7%	75	100.0%	13	0.6065	0.5986
V6	T	9.5%	74	10.7%	14	0.7369	1.0000
V7	G	32.2%	76	53.6%	14	0.0514	<b>0.0409</b>



**EXAMPLE 13: Haplotype analyses**

In addition to the analysis of individual SNPs, haplotype frequencies between the case and control groups were also compared. The haplotypes  
 5 were constructed using a maximum likelihood approach. Existing software for predicting haplotypes was unable to utilize individuals with missing data. Accordingly, a program was developed to make use of all individuals. This allowed more accurate estimates of haplotype frequency. Haplotype analysis based on multiple SNPs in a gene was expected to provide increased evidence  
 10 for an association between a given phenotype and that gene, if all haplotyped SNPs were involved in the characterization of the phenotype. Otherwise, allelic variation involving those haplotyped SNPs would not be associated more significantly with different risks or susceptibilities toward the phenotype.

1. Asthma phenotype: The estimated frequency of each haplotype  
 15 was compared between cases and controls by a permutation test. An overall comparison of the distribution of all haplotypes between the two groups was also performed. In Tables 18, 19, and 20 the haplotype analysis (2-at-a-time) for all SNPs in Gene 216 is presented for the combined, the UK and the US populations, respectively. The diagonal entries represent the single SNP p-  
 20 values. The other entries represent the p-values for a test of association between the asthma phenotype and the four haplotypes defined by the 2 SNPs listed on the horizontal and vertical axes. The frequency of the individual SNPs in the cases and controls are shown at the bottom of the tables. Marked cells indicate p-values that were statistically significant. Medium gray cells represent  
 25 p-values that are less or equal to 0.05 but greater than 0.01, dark gray, boxed cells represent p-values that are less or equal to 0.01 but greater than 0.001, light gray, boxed cells represent p-values that are less or equal to 0.001.

As seen in Table 18, haplotypes defined by SNPs V4 & V1, V-2 & ST+4, V-3 & ST+4, V4 & V2, and V5 & V4, yielded highly significant p-values of  
 30 0.00035, 0.000043, 0.000040, 0.00039 and 0.00026 respectively. These values were more significant than the analysis of these SNPs alone (SNP V5

p = 0.16; V4 p = 0.03; V2 p = 0.16; V1 p = 0.25; V-3 p = 0.68; V-2 p = 0.75; ST+4 p = 0.04). These associations were also more significant than the one observed for the single SNP V-1 reported above. The most significant association in Gene 216 was found in the UK population (Table 19). Five SNP combinations showed significance at the 0.001 level (SNPs V-2 & ST+4 p = 0.000005; ST+5 & ST+4 p = 0.00047; ST+4 & S+1 p = 0.00039; V-3 & ST+4 p = 0.000003, and ST+4 & S2 p = 0.00029; Table 19) in the UK population. Forty SNP combinations were significant at the 0.01 level in Gene 216 in the UK population (Table 19). In the US population, numerous SNP combinations were significant at the 0.01 level for Genes 216 (Table 20).

All SNP combinations in Table 18, 19, and 20 that demonstrated a significant difference ( $p \leq 0.05$ ) in the distribution of frequencies of the four haplotypes between the cases and the control populations were further analyzed to identify individual haplotypes that were also significant. Table 21 presents the haplotypes that were significantly associated, at the 0.05 level of significance, with the asthma phenotype. Haplotypes with higher allele frequency in the case population than in the control population acted as risk factors that increased the susceptibility to asthma. Haplotypes with lower allele frequencies in the case population than in the control population acted as protective factors that decreased the susceptibility to asthma.

In the combined populations, the two most significant haplotypes were protective and contained the C allele at SNP ST+4 in combination with the G allele at SNP V-3 ( $p = 0.00002$ ) or the C allele at SNP V-2 ( $p = 0.00003$ ). Additionally, haplotypes C/C (SNPs ST+4/V-4,  $p = 0.0004$ ) and A/C (SNPs ST+7/V-2,  $p = 0.0005$ ) were protective and significant at the 0.001 level of significance. Five haplotypes involving allele A at SNP ST+4 were susceptibility haplotypes, associated with an increased risk of asthma at the 0.001 level of significance. They were haplotypes C/A (SNPs Q-1/ST+4,  $p = 0.0005$ ), C/A (SNPs KL+2/ST+4,  $p = 0.0007$ ), A/G (SNPs ST+4/ST+7,  $p = 0.0006$ ), A/C (SNPs ST+4/V-1,  $p = 0.0006$ ) and A/C (SNPs ST+4/V4,  $p = 0.001$ ). Other susceptibility haplotypes that were significant at the 0.001 level

were T/G (SNPs Q-1/T+2,  $p < 0.0001$ ), G/A (SNPs T+2/V-1,  $p = 0.0009$ ) and C/C (SNPs V-1/V4,  $p = 0.0009$ ).

A similar pattern was observed in the UK and US populations separately, where haplotypes involving the C allele in SNP ST+4 were protective while haplotypes involving the A allele in SNP ST+4 increased the susceptibility to asthma. In the UK population, the most significant haplotypes were protective and, as in the combined population, were C/G (SNPs ST+4/V-3,  $p = 0.000002$ ) and C/C (SNPs ST+4/V-2,  $p = 0.000003$ ). The following protective haplotypes were significant at the 0.0001 level: T/C (SNPs S+1/ST+4,  $p = 0.0002$ ), C/T (SNPs ST+4/ST+5,  $p = 0.0002$ ), A/C (SNPs ST+7/V-2,  $p = 0.0007$ ), C/C (SNPs ST+4/V-4,  $p = 0.0006$ ), and C/C (SNPs S2/V6,  $p = 0.0008$ ). The susceptibility haplotypes, significant at the 0.001 level, were G/A (SNPs F+1/ST+4,  $p = 0.0002$ ), G/A (SNPs S1/ST+4,  $p = 0.0005$ ), G/A (SNPs S2/ST+4,  $p = 0.0001$ ), C/A (SNPs Q-1/ST+4,  $p = 0.0006$ ), C/A (SNPs KL+2/ST+4,  $p = 0.0008$ ), AG (SNPs ST+4/ST+7,  $p = 0.0008$ ), T/G (SNPs Q-1/T+2,  $p = 0.0001$ ), G/C (SNPs L-1/V-1,  $p = 0.0009$ ), A/C (SNPs ST+4/V-1,  $p = 0.0008$ ), A/C (SNPs ST+4/V7,  $p < 0.0001$ ) and A/C (SNPs ST+4/V4,  $p = 0.0004$ ). In the US population, four susceptibility haplotypes involving allele A at SNP I1 were significant at the 0.001 level: A/A (SNPs I1/ST+4,  $p = 0.0004$ ), A/T (SNPs I1/V3,  $p = 0.0009$ ), A/C (SNPs I1/V2,  $p = 0.0009$ ) and A/A (SNPs I1/V1,  $p = 0.0006$ ).

In addition, haplotypes consisting of SNPs present in the mature mRNA were analyzed. Table 22 presents the 15-SNP haplotypes (for SNPs D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7) in the combined and separate UK and US populations. In the combined populations, four haplotypes (T/A/A/C/G/C/T/C/A/C/C/G/A/C/C, T/A/G/C/A/C/T/C/A/C/T/G/A/C/G, T/A/G/C/G/G/T/C/A/C/T/C/A/C/C, and T/G/A/C/G/C/T/C/T/T/C/G/G/C/G) were significant at the 0.05 level. In the UK population, two haplotypes (T/A/G/C/A/C/T/C/A/C/T/G/A/C/G and T/A/G/C/G/G/T/C/A/C/T/C/A/C/G) were significant at the 0.05 level, and one (T/A/G/C/G/G/T/C/A/C/T/C/A/C/C) was significant at the 0.003 level. In the US population, three haplotypes

(T/A/A/C/G/C/C/T/A/C/T/C/A/T/G, T/A/G/C/G/G/T/C/A/C/T/G/A/C/C, and T/G/A/C/G/C/T/C/T/T/C/G/G/C/G) and the overall test were significant at the 0.05 level.

2. Bronchial Hyper-responsiveness: A similar test for association of 2-SNP-at-a-time haplotypes with BHR ( $PC_{20} \leq 16$  mg/ml) was performed. In Tables 23, 24, and 25, the haplotype analysis (2-at-a-time) for all SNPs in Gene 216 is presented for the combined US and UK populations, the UK population, and the US population, respectively. Two SNP combinations in Gene 216 were significant at the 0.01 level in the combined sample (Table 23: SNPs V-2 & ST+4,  $p = 0.0038$ , and SNPs V-3 & ST+4,  $p = 0.0042$ ). In contrast, in the UK population, twenty-seven SNP combinations were significant at the 0.01 level in Gene 216 (Table 24). In the US population, ten SNP combinations were significant at the 0.01 level in Gene 216 (Table 25). Tables 18, 19, and 20 and Tables 23, 24, and 25 showed similar patterns of significance with lower level achieved in the BHR analysis due to the reduced sample size in the ( $PC_{20} \leq 16$  mg/ml) subgroup.

All SNP combinations in Table 23, 24, and 25, that demonstrated a significant difference ( $p \leq 0.05$ ) in the distribution of frequencies of the four haplotypes between the cases and the control populations, were further analyzed to identify individual haplotypes that were also significant. Table 26 presents the haplotypes that were significantly associated, at the 0.05 level of significance, with the BHR phenotype. In the combined populations, the two most significant haplotypes were protective and contained the C allele in SNP ST+4 in combination with the G allele at SNP V-3 ( $p = 0.0025$ ) or the C allele at SNP V-2 ( $p = 0.0022$ ). In the UK population, the most significant haplotypes, A/A (SNPs S1/S+1,  $p = 0.0001$ ) and T/G (SNPs Q-1/T+2,  $p = 0.0003$ ), increased the susceptibility toward BHR. The protective haplotype C/T (SNPs S2/T+2) was significant at the 0.001 level. Due to the smaller sample size in the US population, no haplotype was significantly associated with BHR at the 0.001 level.

As for the asthma yes/no phenotype, we analyzed haplotypes consisting

of SNPs present in the mature mRNA. Table 27 presents the 15-SNP haplotypes (for SNPs D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/ V6/V7) in the combined and separate UK and US populations. In the combined populations, one haplotype (T/G/A/C/G/C/T/C/T/T/C/G/G/C/G) was significant at the 0.05  
 5 significance level. In the UK population, one haplotype (T/A/G/C/G/G/T/C/A/C/T/C/A/C/G) was significant at the 0.05 level. In the US population, three haplotypes (T/A/A/C/G/C/C/C/A/C/T/C/A/C/G, T/A/A/C/G/C/C/T/A/C/T/C/A/C/G and T/A/G/C/G/G/T/C/A/C/T/G/A/T/G) were significant at the 0.05 level.

10 It is noted that for Tables 21, 22, 26, and 27, the haplotypes are written without slashes separating each allele. Thus, the haplotype that is T/G/A/C/G/C/T/C/T/T/C/G/G/C/G is written as TGACGCTCTTCGGCG in Table 27. This represents the short-hand designations for the haplotypes and is not, in any way, meant to represent contiguous nucleotide sequences.

15 In summary, haplotype analysis of SNPs significantly strengthened the evidence in support of Gene 216 as an asthma susceptibility gene. In some SNP combinations, the association was increased by an order of magnitude. The most striking association again appeared in the 3' region of the gene, in agreement with the single SNP analysis.

20

TABLE 18

	A-1	D-2	D-1	D1	F1	F+1	G-1	I1	KL+1	KL+2	I-2	L-1
A-1	0.8039	0.9127	0.7308	0.4924	0.9768	0.9879	0.9481	0.9742	0.8508	0.2703	0.9889	0.9949
D-2	.	1	0.773	0.4976	0.9639	0.9684	0.9684	0.9723	0.8281	0.2843	0.9592	0.4749
D-1	.	.	0.4449	0.3024	0.7604	0.1073	0.5154	0.6127	0.7815	0.1017	0.628	0.9495
D1	.	.	.	0.3786	0.6014	0.1323	0.5151	0.5816	0.3315	0.0656	0.5442	0.5749
F1	.	.	.	.	1	0.3471	0.9912	0.9883	0.5563	0.3923	0.9623	0.9874
F+1	.	.	.	.	.	0.1913	0.2041	0.3653	0.4372	0.1921	0.4026	0.3823
G-1	.	.	.	.	.	.	0.89	0.9235	0.6736	0.2052	0.9659	0.9721
I1	.	.	.	.	.	.	.	0.9724	0.8784	0.3152	0.9669	0.9797
KL+1	.	.	.	.	.	.	.	.	0.5223	0.333	0.7769	0.7579
KL+2	.	.	.	.	.	.	.	.	.	0.1085	0.1921	0.2179
L-2	.	.	.	.	.	.	.	.	.	.	1	0.9911
L-1	.	.	.	.	.	.	.	.	.	.	.	1
L1	.	.	.	.	.	.	.	.	.	.	.	.
M+1	.	.	.	.	.	.	.	.	.	.	.	.
Q-1	.	.	.	.	.	.	.	.	.	.	.	.
S1	.	.	.	.	.	.	.	.	.	.	.	.
S2	.	.	.	.	.	.	.	.	.	.	.	.
S+1	.	.	.	.	.	.	.	.	.	.	.	.
ST+4	.	.	.	.	.	.	.	.	.	.	.	.
ST+5	.	.	.	.	.	.	.	.	.	.	.	.
ST+6	.	.	.	.	.	.	.	.	.	.	.	.
ST+7	.	.	.	.	.	.	.	.	.	.	.	.
T1	.	.	.	.	.	.	.	.	.	.	.	.
T2	.	.	.	.	.	.	.	.	.	.	.	.
T+1	.	.	.	.	.	.	.	.	.	.	.	.
T+2	.	.	.	.	.	.	.	.	.	.	.	.
V-4	.	.	.	.	.	.	.	.	.	.	.	.
V-3	.	.	.	.	.	.	.	.	.	.	.	.
V-2	.	.	.	.	.	.	.	.	.	.	.	.
V-1	.	.	.	.	.	.	.	.	.	.	.	.
V1	.	.	.	.	.	.	.	.	.	.	.	.
V2	.	.	.	.	.	.	.	.	.	.	.	.
V3	.	.	.	.	.	.	.	.	.	.	.	.
V4	.	.	.	.	.	.	.	.	.	.	.	.
V5	.	.	.	.	.	.	.	.	.	.	.	.
V6	.	.	.	.	.	.	.	.	.	.	.	.
V7	.	.	.	.	.	.	.	.	.	.	.	.
CNTL	2.4%	0.7%	62.5%	0.0%	96.8%	65.2%	90.7%	84.9%	96.1%	71.3%	92.9%	86.9%
CASE	2.7%	0.8%	65.7%	0.4%	96.9%	70.4%	91.3%	85.3%	97.2%	77.1%	93.1%	89.2%



**TABLE 18 (CON'T)**

T+2	V-4	V-3	V-2	V-1	V1	V2	V3	V4	V5	V6	V7
0.79	0.7392	0.9684	0.9735	0.0152	0.5549	0.3121	0.9772	0.1757	0.2634	0.8803	0.4577 A-1
0.6779	0.8285	0.8657	0.9063	0.0237	0.3973	0.2662	0.9391	0.1042	0.2629	0.9316	0.3781 D-2
0.7279	0.6032	0.4248	0.3745	0.0114	0.5582	0.327	0.8431	0.0108	0.283	0.6311	0.2906 D-1
0.458	0.3022	0.4182	0.4521	0.0037	0.1327	0.0675	0.5428	0.0241	0.0722	0.4411	0.1348 D1
0.9588	0.8852	0.9097	0.9512	0.0044	0.0383	0.0792	0.6758	0.0124	0.1615	0.4072	0.6354 F1
0.5501	0.2282	0.2602	0.2543	0.0259	0.2113	0.1309	0.498	0.1238	0.2147	0.2625	0.4639 F+1
0.9795	0.0428	0.3054	0.2088	0.0289	0.651	0.3589	0.9771	0.2069	0.3703	0.8719	0.5943 G-1
0.9446	0.8756	0.8216	0.9761	0.0378	0.5968	0.3542	0.9972	0.1146	0.3591	0.9877	0.4402 I-1
0.7011	0.7603	0.7294	0.7631	0.0325	0.4238	0.3076	0.7548	0.0056	0.4411	0.3191	0.495 KL+1
0.1919	0.0736	0.4004	0.0503	0.0336	0.2202	0.1035	0.1544	0.0371	0.0992	0.2324	0.2054 KL+2
0.9093	0.9508	0.2241	0.2065	0.0185	0.4775	0.2481	0.983	0.0961	0.3002	0.5981	0.3571 L-2
0.9541	0.7599	0.9319	0.8742	0.0162	0.4429	0.2307	0.993	0.1275	0.2329	0.5903	0.5975 L-1
0.9565	0.3694	0.6732	0.6976	0.0168	0.4127	0.2653	0.3879	0.1228	0.2634	0.7962	0.4232 L-1
0.9534	0.7717	0.9269	0.8813	0.0193	0.4496	0.2396	0.9881	0.1257	0.2368	0.2557	0.3377 M+1
0.0087	0.0904	0.0311	0.0312	0.0652	0.0485	0.0435	0.1078	0.0056	0.0601	0.0568	0.0836 Q-1
0.0308	0.0575	0.0685	0.0649	0.0139	0.0365	0.0356	0.0467	0.1243	0.0154	0.0578	0.1079 S-1
0.1231	0.2415	0.1827	0.2652	0.0206	0.1263	0.0872	0.2356	0.0933	0.1277	0.0359	0.3023 S-2
0.8895	0.9886	0.8774	0.9288	0.0259	0.5414	0.3325	0.9122	0.1384	0.3162	0.8937	0.0726 S+1
0.08	0.00156	0.00004	0.000043	0.0018	0.0759	0.0464	0.0543	0.0048	0.0644	0.0699	0.0626 ST+4
0.8158	0.5208	0.4306	0.6336	0.0193	0.4253	0.2372	0.7059	0.0527	0.3998	0.6264	0.1011 ST+5
0.8576	0.6143	0.5272	0.8302	0.0214	0.4174	0.28	0.9429	0.1547	0.2775	0.6931	0.4634 ST+6
0.0261	0.0719	0.0094	0.0005	0.0163	0.0362	0.0281	0.065	0.0463	0.0431	0.0212	0.061 ST+7
0.9379	0.7097	0.9318	0.5077	0.0193	0.4368	0.2472	0.9753	0.1363	0.2445	0.347	0.4723 T-1
0.8158	0.5744	0.7118	0.4396	0.022	0.409	0.2221	0.8393	0.0981	0.2196	0.5731	0.1754 T-2
0.828	0.5597	0.6895	0.1927	0.0142	0.4427	0.2221	0.9308	0.1242	0.2337	0.9034	0.5446 T+1
0.8076	0.8012	0.7834	0.8324	0.0065	0.3585	0.1573	0.9334	0.0844	0.1444	0.841	0.5857 T+2
	0.4473	0.5684	0.5259	0.0173	0.4201	0.2134	0.6449	0.1279	0.2684	0.7743	0.3092 V-4
				0.0186	0.4491	0.2377	0.6559	0.1395	0.2424	0.9693	0.2688 V-3
		0.6834	0.472	0.0214	0.4646	0.242	0.6802	0.1556	0.2667	0.9625	0.3059 V-2
					0.0055	0.0184	0.0173	0.036	0.00128	0.0206	0.0201
						0.2515	0.1198	0.3907	0.00035	0.3308	0.297
							0.1576	0.2471	0.00038	0.3577	0.199 V-2
							0.9235	0.0709	0.3473	0.7892	0.4611 V-3
									0.00026	0.0876	0.1291 V-4
									0.0336	0.1568	0.1984 V-5
										0.1576	0.1903 V-6
										0.7841	0.2029 V-7
										</	



TABLE 19

A-1	D-2	D-1	D1	F1	F+1	G-1	I1	KL+1	KL+2	L-2	L-1
A-1	0.111	0.2613	0.1922	0.0675	0.2602	0.0254	0.2529	0.0665	0.2105	0.0285	0.2495
D-2	.	1	0.584	0.5053	0.9386	0.0637	0.9852	0.4017	0.8484	0.1957	0.9386
D-1	.	.	0.3807	0.2993	0.6333	0.0598	0.4142	0.1335	0.5902	0.0581	0.542
D1	.	.	.	0.428	0.7212	0.0221	0.672	0.0705	0.457	0.0436	0.8578
F1	.	.	.	.	.	0.071	0.9828	0.201	0.7047	0.2499	0.9768
F+1	.	.	.	.	1	0.0295	0.0361	0.1094	0.0838	0.0456	0.0428
G-1	.	.	.	.	.	.	1	0.421	0.6772	0.1679	0.9918
I1	.	.	.	.	.	.	.	0.1094	0.2257	0.0304	0.2741
KL+1	.	.	.	.	.	.	.	.	0.7685	0.2937	0.7289
KL+2	.	.	.	.	.	.	.	.	.	0.1177	0.0143
L-2	.	.	.	.	.	.	.	.	.	0.8633	0.2343
L-1	.	.	.	.	.	.	.	.	.	.	0.0992
L1	.	.	.	.	.	.	.	.	.	.	.
M+1	.	.	.	.	.	.	.	.	.	.	.
Q-1	.	.	.	.	.	.	.	.	.	.	.
S1	.	.	.	.	.	.	.	.	.	.	.
S2	.	.	.	.	.	.	.	.	.	.	.
S+1	.	.	.	.	.	.	.	.	.	.	.
ST+4	.	.	.	.	.	.	.	.	.	.	.
ST+5	.	.	.	.	.	.	.	.	.	.	.
ST+6	.	.	.	.	.	.	.	.	.	.	.
ST+7	.	.	.	.	.	.	.	.	.	.	.
T1	.	.	.	.	.	.	.	.	.	.	.
T2	.	.	.	.	.	.	.	.	.	.	.
T+1	.	.	.	.	.	.	.	.	.	.	.
T+2	.	.	.	.	.	.	.	.	.	.	.
V-4	.	.	.	.	.	.	.	.	.	.	.
V-3	.	.	.	.	.	.	.	.	.	.	.
V-2	.	.	.	.	.	.	.	.	.	.	.
V-1	.	.	.	.	.	.	.	.	.	.	.
V1	.	.	.	.	.	.	.	.	.	.	.
V2	.	.	.	.	.	.	.	.	.	.	.
V3	.	.	.	.	.	.	.	.	.	.	.
V4	.	.	.	.	.	.	.	.	.	.	.
V5	.	.	.	.	.	.	.	.	.	.	.
V6	.	.	.	.	.	.	.	.	.	.	.
V7	.	.	.	.	.	.	.	.	.	.	.
ONTL	1.1%	0.7%	61.1%	0.0%	97.9%	64.1%	90.2%	83.7%	97.1%	71.6%	92.7%
CASE	3.4%	1.0%	65.5%	0.5%	98.0%	74.2%	90.1%	89.2%	98.0%	79.1%	92.3%

**TABLE 19 (CON'T)**

TABLE 19 (CONT.)

T+2	V+4	V+3	V+2	V+1	V1	V2	V3	V4	V5	V6	V7
0.28	0.2117	0.1889	0.2111	0.0044	0.203	0.1245	0.2861	0.0349	0.1471	0.1944	0.0648 A-1
0.8827	0.9002	0.8742	0.8947	0.0369	0.8276	0.4874	0.8564	0.0915	0.546	0.8498	0.1955 D-2
0.5228	0.2782	0.1773	0.1909	0.0136	0.5732	0.343	0.2537	0.0208	0.4448	0.4875	0.1571 D-1
0.7043	0.5213	0.4693	0.4989	0.0065	0.412	0.1691	0.5155	0.0201	0.2686	0.4573	0.0498 D1
0.943	0.8506	0.9194	0.9548	0.0228	0.6878	0.3354	0.7344	0.0484	0.3653	0.9382	0.1597 F1
0.1249	0.0101	0.0113	0.0087	0.013	0.0618	0.0451	0.0966	0.0345	0.0629	0.0278	0.0753 F+1
0.9858	0.2977	0.8438	0.6792	0.0415	0.9855	0.6849	0.9726	0.1414	0.8025	0.9053	0.2086 G-1
0.2177	0.3533	0.246	0.3401	0.0177	0.2126	0.1802	0.2426	0.0312	0.2039	0.3763	0.2233 I1
0.7327	0.8669	0.8616	0.9191	0.0265	0.2687	0.1975	0.7823	0.071	0.2077	0.6468	0.3125 KL+1
0.1442	0.0724	0.0162	0.0244	0.0552	0.2537	0.1109	0.1717	0.043	0.2005	0.1548	0.0756 KL+2
0.7077	0.2281	0.6131	0.6079	0.0351	0.9322	0.5697	0.9462	0.0829	0.642	0.7995	0.0686 L-2
0.2028	0.2661	0.2469	0.3104	0.0034	0.1807	0.086	0.1975	0.014	0.1155	0.308	0.2453 L-1
0.9395	0.5718	0.933	0.9401	0.0272	0.8019	0.4718	0.5164	0.1216	0.5559	0.8265	0.1871 L1
0.2275	0.2806	0.2715	0.3304	0.0039	0.1989	0.1001	0.2133	0.0133	0.135	0.1571	0.1289 M+1
0.0054	0.1811	0.0307	0.0371	0.0153	0.0954	0.0819	0.1582	0.0577	0.0899	0.0901	0.0757 Q-1
0.0263	0.0643	0.0622	0.0672	0.03	0.0782	0.0444	0.049	0.0842	0.0488	0.066	0.0456 S1
0.0116	0.0243	0.0102	0.0196	0.0078	0.0172	0.0152	0.0291	0.0127	0.0146	0.0127	0.0296 S2
0.8376	0.4732	0.2745	0.3238	0.02	0.8835	0.5525	0.8892	0.0901	0.7007	0.7387	0.0595 S+1
0.0358	0.0028	0.00003	0.000005	0.0025	0.0644	0.0448	0.0386	0.00223	0.0624	0.1528	0.005 ST+4
0.4405	0.1723	0.0719	0.1069	0.0176	0.5012	0.2728	0.7302	0.0213	0.358	0.3928	0.0425 ST+5
0.2789	0.2248	0.2441	0.2223	0.003	0.243	0.0759	0.2309	0.0126	0.1116	0.2151	0.0288 ST+6
0.1174	0.0502	0.0113	0.0068	0.0302	0.1588	0.1099	0.211	0.0575	0.125	0.0736	0.1204 ST+7
0.2822	0.3174	0.3134	0.2897	0.0031	0.2313	0.1424	0.2415	0.0192	0.1615	0.2509	0.1387 T1
0.7364	0.7594	0.7447	0.5181	0.0224	0.5922	0.3155	0.5732	0.0534	0.4225	0.6846	0.1533 V7
0.2704	0.5154	0.4684	0.1882	0.0085	0.3211	0.174	0.3964	0.0238	0.2236	0.4702	0.1991 T+1
1	0.9351	0.8843	0.913	0.0075	0.6584	0.2466	0.5827	0.0473	0.4298	0.7111	0.2678 T+2
0.7529	0.7963	0.8142	0.0289	0.0289	0.865	0.3998	0.4783	0.0782	0.5556	0.6443	0.0393 V-4
0.0311	0.0311	0.0311	0.0311	0.0311	0.8463	0.4855	0.9007	0.0453	0.638	0.9052	0.0242 V-3
0.0281	0.0281	0.0281	0.0281	0.0281	0.8731	0.5203	0.8191	0.0594	0.7102	0.8811	0.0258 V-2
0.0105	0.0105	0.0105	0.0105	0.0105	0.0288	0.0292	0.0615	0.0306	0.0291	0.0295	0.0352 V-1
0.7385	0.7385	0.7385	0.7385	0.7385	0.3169	0.753	0.753	0.0166	0.2334	0.8318	0.1852 V1
0.476	0.476	0.476	0.476	0.476	0.3129	0.7301	0.7301	0.027	0.3617	0.4953	0.1371 V2
0.0491	0.0491	0.0491	0.0491	0.0491	0.5463	0.855	0.855	0.0491	0.5463	0.855	0.1894 V3
0.0053	0.0053	0.0053	0.0053	0.0053	0.012	0.0853	0.0252	0.012	0.0853	0.0252	0.0252 V4
0.5467	0.5467	0.5467	0.5467	0.5467	0.3688	0.5467	0.5467	0.3688	0.5467	0.5467	0.141 V5
0.6308	0.6308	0.6308	0.6308	0.6308	0.0596	0.0596	0.0596	0.0596	0.0596	0.0596	0.0333 V6
0.0596	0.0596	0.0596	0.0596	0.0596	0.0596	0.0596	0.0596	0.0596	0.0596	0.0596	0.0596 V7
87.5%	25.2%	38.1%	37.5%	86.4%	97.8%	97.5%	78.5%	75.4%	97.1%	8.3%	65.5% CNIL
87.5%	26.7%	40.2%	39.3%	93.8%	98.5%	99.0%	80.1%	83.7%	98.5%	9.6%	74.3% CASE

TABLE 20

A-1	D-2	D-1	D1	F1	F+1	G-1	It	KL+1	KL+2	L-2	L-1
A-1	0.1853	0.1235	0.2535	0.1148	0.2394	0.1529	0.1258	0.0046	0.3081	0.2147	0.1031
A-2	.	1	0.9802	0.7288	0.7249	0.4015	0.4532	0.0116	0.9659	0.8832	0.5436
D-1	.	.	1	0.8612	0.8462	0.2524	0.4825	0.0121	0.986	0.9531	0.6891
D1	.	.	.	1	0.6682	0.2231	0.2307	0.006	0.9992	0.8404	0.3995
F1	.	.	.	.	0.5136	0.4909	0.4359	0.0227	0.7965	0.8546	0.5584
F+1	.	.	.	.	.	0.2401	0.2357	0.0317	0.6219	0.3717	0.1716
G-1	.	.	.	.	.	.	0.3635	0.0287	0.5034	0.3104	0.0311
It	.	.	.	.	.	.	.	0.0105	0.0228	0.0113	0.03
KL+1	.	.	.	.	.	.	.	1	0.9662	0.6992	0.043
KL+2	.	.	.	.	.	.	.	.	0.8614	0.75	0.0217
L-2	.	.	.	.	.	.	.	.	.	0.7362	0.0435
L-1	.	.	.	.	.	.	.	.	.	.	0.0116
L1	.	.	.	.	.	.	.	.	.	.	.
M+1	.	.	.	.	.	.	.	.	.	.	.
Q-1	.	.	.	.	.	.	.	.	.	.	.
S1	.	.	.	.	.	.	.	.	.	.	.
S2	.	.	.	.	.	.	.	.	.	.	.
S+1	.	.	.	.	.	.	.	.	.	.	.
ST+4	.	.	.	.	.	.	.	.	.	.	.
ST+5	.	.	.	.	.	.	.	.	.	.	.
ST+6	.	.	.	.	.	.	.	.	.	.	.
ST+7	.	.	.	.	.	.	.	.	.	.	.
T1	.	.	.	.	.	.	.	.	.	.	.
T2	.	.	.	.	.	.	.	.	.	.	.
T+1	.	.	.	.	.	.	.	.	.	.	.
T+2	.	.	.	.	.	.	.	.	.	.	.
V-4	.	.	.	.	.	.	.	.	.	.	.
V-3	.	.	.	.	.	.	.	.	.	.	.
V-2	.	.	.	.	.	.	.	.	.	.	.
V-1	.	.	.	.	.	.	.	.	.	.	.
V1	.	.	.	.	.	.	.	.	.	.	.
V2	.	.	.	.	.	.	.	.	.	.	.
V3	.	.	.	.	.	.	.	.	.	.	.
V4	.	.	.	.	.	.	.	.	.	.	.
V5	.	.	.	.	.	.	.	.	.	.	.
V6	.	.	.	.	.	.	.	.	.	.	.
V7	.	.	.	.	.	.	.	.	.	.	.
CNTL	4.6%	0.7%	86.0%	0.0%	94.8%	67.4%	91.8%	87.2%	94.2%	70.8%	93.3%
CASE	0.0%	0.0%	86.7%	0.0%	92.6%	57.4%	96.2%	70.4%	94.2%	69.2%	96.3%
											92.0%
											77.8%





**TABLE 21**

Asthma Yes/No Combined US and UK				
SNP COMBINATION	HAPLOTYPE	FREQUENCIES		P-VALUE
		CNTL	CASE	
D1/ST+4	TA	0.5146	0.5969	0.0442
D1/ST+4	TC	0.4854	0.3992	0.0376
F+1/ST+4	GA	0.3080	0.4291	0.0038
S+1/ST+4	TC	0.0818	0.0188	0.0013
S1/ST+4	AA	0.1018	0.0538	0.0321
S1/ST+4	GA	0.4171	0.5466	0.0012
S2/ST+4	GA	0.3117	0.4293	0.0019
Q-1/ST+4	CA	0.4091	0.5503	<b>0.0005</b>
Q-1/ST+4	TA	0.1069	0.0506	0.0201
KL+2/ST+4	AA	0.1084	0.0519	0.0362
KL+2/ST+4	CA	0.4048	0.5487	<b>0.0007</b>
KL+2/ST+4	CC	0.3082	0.2234	0.0214
ST+4/ST+5	CT	0.0475	0.0132	0.0209
S1/ST+5	AT	0.1050	0.0539	0.0228
S2/ST+5	CT	0.1322	0.0638	0.0184
S2/ST+5	GT	0.3319	0.4252	0.0250
Q-1/ST+5	CT	0.3449	0.4328	0.0229
Q-1/ST+5	TT	0.1193	0.0554	0.0099
KL+2/ST+5	AT	0.1342	0.0482	0.0049
KL+2/ST+5	CT	0.3301	0.4415	0.0088
A-1/ST+7	AA	0.2149	0.1423	0.0187
A-1/ST+7	AG	0.7615	0.8307	0.0357
D-1/ST+7	CA	0.1228	0.0453	0.0055
D-1/ST+7	CG	0.5013	0.6110	0.0122
D1/ST+7	TA	0.2186	0.1423	0.0142
D1/ST+7	TG	0.7814	0.8539	0.0186
F1/ST+7	AA	0.1861	0.1246	0.0356
F1/ST+7	AG	0.7816	0.8446	0.0455
F1/ST+7	GG	0.0000	0.0132	0.0465
G-1/ST+7	TA	0.1459	0.0748	0.0073
G-1/ST+7	TG	0.7598	0.8370	0.0165
M+1/ST+7	GA	0.2177	0.1424	0.0165
M+1/ST+7	GG	0.6700	0.7469	0.0326
L-2/ST+7	GA	0.1495	0.0731	0.0020
L-2/ST+7	GG	0.7791	0.8582	0.0096
L1/ST+7	CA	0.2186	0.1423	0.0132
L1/ST+7	CG	0.7745	0.8539	0.0100
ST+4/ST+7	AA	0.1108	0.0542	0.0328

ST+4/ST+7	AG	0.4038	0.5472	<b>0.0006</b>
ST+5/ST+7	TA	0.1266	0.0486	0.0033
ST+5/ST+7	TG	0.3376	0.4395	0.0089
ST+6/ST+7	CA	0.2140	0.1392	0.0170
ST+6/ST+7	CG	0.7814	0.8530	0.0225
S+1/ST+7	TA	0.1504	0.0594	0.0013
S+1/ST+7	TG	0.3363	0.4154	0.0441
S1/ST+7	AA	0.1036	0.0564	0.0381
S1/ST+7	GG	0.7822	0.8546	0.0213
S2/ST+7	CA	0.1481	0.0743	0.0089
Q-1/ST+7	TA	0.1473	0.0750	0.0054
Q-1/ST+7	CG	0.7802	0.8424	0.0487
Q-1/ST+7	TG	0.0025	0.0128	0.0325
F+1/S+1	AT	0.1660	0.0750	0.0093
S2/S+1	CT	0.1628	0.0702	0.0034
Q-1/S+1	TT	0.1405	0.0646	0.0041
KL+2/S+1	AT	0.1379	0.0456	0.0026
D-1/S1	CA	0.1057	0.0538	0.0229
D-1/S1	GA	0.0000	0.0000	0.0013
D-1/S1	CG	0.5192	0.6025	0.0430
D1/S1	TA	0.1053	0.0538	0.0224
D1/S1	TG	0.8947	0.9423	0.0349
L-2/S1	AA	0.0000	0.0040	0.0027
L-2/S1	GA	0.1056	0.0499	0.0150
L-2/S1	GG	0.8239	0.8814	0.0435
KL+1/S1	GA	0.1052	0.0536	0.0215
KL+1/S1	GG	0.8557	0.9184	0.0162
KL+2/S1	AA	0.1056	0.0543	0.0223
D-1/S2	CC	0.1249	0.0508	0.0120
D-1/S2	CG	0.4996	0.5940	0.0293
ST+4/T+1	CT	0.0300	0.0000	0.0182
ST+7/T+1	AC	0.2182	0.1424	0.0140
ST+7/T+1	GC	0.6704	0.7450	0.0387
S1/T+1	AC	0.1057	0.0475	0.0111
S1/T+1	AT	0.0000	0.0063	0.0178
ST+7/T+2	AG	0.0000	0.0000	0.0478
ST+7/T+2	AT	0.2189	0.1418	0.0128
ST+7/T+2	GT	0.6636	0.7475	0.0173
S1/T+2	AG	0.0000	0.0054	0.0151
S1/T+2	AT	0.1052	0.0485	0.0107
S1/T+2	GT	0.7773	0.8408	0.0352
Q-1/T+2	TG	0.0000	0.0142	<b>&lt;0.0001</b>
Q-1/T+2	CT	0.7327	0.8157	0.0114
Q-1/T+2	TT	0.1498	0.0736	0.0034
S2/T2	CC	0.1690	0.0942	0.0082



A-1/V-1	AA	0.1418	0.0763	0.0123
A-1/V-1	AC	0.8346	0.8967	0.0291
D-1/V-1	CA	0.1288	0.0478	0.0046
D-1/V-1	CC	0.4959	0.6089	0.0104
D-2/V-1	CA	0.1482	0.0763	0.0067
D-2/V-1	CC	0.8448	0.9158	0.0093
D1/V-1	TA	0.1481	0.0763	0.0062
D1/V-1	TC	0.8519	0.9198	0.0088
F+1/V-1	AA	0.1451	0.0763	0.0094
F1/V-1	AA	0.1158	0.0579	0.0187
F1/V-1	AC	0.8520	0.9114	0.0302
F1/V-1	GC	0.0000	0.0123	0.0496
G-1/V-1	TA	0.1424	0.0763	0.0106
G-1/V-1	TC	0.7649	0.8372	0.0228
I1/V-1	GA	0.1187	0.0526	0.0093
M+1/V-1	GA	0.1482	0.0749	0.0046
M+1/V-1	TA	0.0000	0.0014	0.0222
M+1/V-1	GC	0.7393	0.8144	0.0289
L-1/V-1	AA	0.0000	0.0013	0.0077
L-1/V-1	GA	0.1482	0.0751	0.0053
L-1/V-1	GC	0.7411	0.8133	0.0306
L-2/V-1	GA	0.1478	0.0745	0.0047
L-2/V-1	GC	0.7815	0.8568	0.0172
L1/V-1	CA	0.1482	0.0763	0.0043
L1/V-1	CC	0.8449	0.9198	0.0040
ST+4/V-1	AA	0.1078	0.0529	0.0245
ST+4/V-1	AC	0.4083	0.5477	<b>0.0006</b>
ST+5/V-1	TA	0.1199	0.0600	0.0155
ST+5/V-1	TC	0.3443	0.4280	0.0306
ST+6/V-1	CA	0.1463	0.0729	0.0043
ST+6/V-1	CC	0.8491	0.9194	0.0070
ST+7/V-1	AA	0.1490	0.0763	0.0057
ST+7/V-1	GC	0.7827	0.8547	0.0188
S+1/V-1	TA	0.1412	0.0763	0.0129
S1/V-1	AA	0.1046	0.0594	0.0469
S1/V-1	GC	0.8523	0.9237	0.0042
S2/V-1	CA	0.1475	0.0763	0.0057
T+1/V-1	CA	0.1482	0.0744	0.0042
T+1/V-1	TA	0.0000	0.0019	0.0089
T+1/V-1	CC	0.7386	0.8128	0.0280
T+2/V-1	GA	0.0000	0.0064	<b>0.0009</b>
T+2/V-1	TA	0.1482	0.0700	0.0015
T+2/V-1	TC	0.7342	0.8193	0.0076
T1/V-1	CA	0.0000	0.0003	0.0194
T1/V-1	TA	0.1482	0.0760	0.0050

T1/V-1	TC	0.7389	0.8057	0.0467
T2/V-1	CA	0.1482	0.0763	0.0057
V-2/V-1	CA	0.1475	0.0763	0.0056
V-3/V-1	GA	0.1475	0.0763	0.0048
V-4/V-1	CA	0.1475	0.0763	0.0074
Q-1/V-1	TA	0.1475	0.0763	0.0057
Q-1/V-1	CC	0.8502	0.9122	0.0183
KL+1/V-1	GA	0.1115	0.0567	0.0176
KL+1/V-1	GC	0.8494	0.9153	0.0129
KL+2/V-1	AA	0.1157	0.0573	0.0153
KL+2/V-1	CC	0.6805	0.7530	0.0401
ST+4/V-2	AC	0.5145	0.5990	0.0390
ST+4/V-2	CC	0.1137	0.0232	<b>0.00003</b>
ST+7/V-2	AC	0.1672	0.0700	<b>0.0005</b>
ST+7/V-2	GC	0.4655	0.5494	0.0449
Q-1/V-2	TC	0.1461	0.0713	0.0056
ST+4/V-3	CG	0.1118	0.0233	<b>0.00002</b>
ST+7/V-3	AG	0.1629	0.0675	0.0013
Q-1/V-3	TG	0.1460	0.0701	0.0049
KL+2/V-3	AG	0.1262	0.0513	0.0071
G-1/V-4	CC	0.0387	0.0050	0.0130
ST+4/V-4	AC	0.5160	0.5966	0.0489
ST+4/V-4	CC	0.2409	0.1311	<b>0.0004</b>
ST+7/V-4	AC	0.1671	0.0786	0.0029
V-1/V7	AG	0.1425	0.0763	0.0103
ST+7/V6	AC	0.1413	0.0752	0.0128
S2/V6	CC	0.2563	0.1671	0.0083
S2/V6	GC	0.6570	0.7374	0.0295
V-1/V6	AC	0.1478	0.0763	0.0065
ST+7/V5	AA	0.1839	0.1256	0.0427
ST+7/V5	GA	0.7788	0.8578	0.0103
S1/V5	AA	0.1048	0.0538	0.0257
S1/V5	GA	0.8580	0.9306	0.0044
V-1/V5	AA	0.1132	0.0594	0.0185
V-1/V5	CA	0.8494	0.9237	0.0039
V4/V5	CA	0.7345	0.8359	0.0022
V4/V5	GA	0.2283	0.1481	0.0112
V4/V5	CG	0.0328	0.0000	0.0083
D-1/V4	CC	0.5072	0.6171	0.0147
D-1/V4	CG	0.1178	0.0423	0.0048
D1/V4	TC	0.7673	0.8321	0.0404
D1/V4	TG	0.2327	0.1641	0.0275
F1/V4	AC	0.7379	0.8223	0.0099
F1/V4	AG	0.2299	0.1469	0.0079
F1/V4	GG	0.0029	0.0172	0.0386

ST+4/V4	AC	0.4053	0.5468	<b>0.0010</b>
ST+4/V4	AG	0.1086	0.0548	0.0467
ST+7/V4	GC	0.6602	0.7614	0.0046
V-1/V4	AC	0.0423	0.0042	0.0035
V-1/V4	CC	0.7250	0.8317	<b>0.0009</b>
V2/V4	CC	0.7358	0.8359	0.0023
V2/V4	TC	0.0315	0.0000	0.0075
V2/V4	CG	0.2270	0.1485	0.0111
V1/V4	AC	0.7369	0.8359	0.0024
V1/V4	TC	0.0304	0.0000	0.0091
V1/V4	AG	0.2277	0.1450	0.0078
Q-1/V4	CC	0.7226	0.8276	0.0016
Q-1/V4	TC	0.0446	0.0083	0.0063
KL+1/V4	GC	0.7324	0.8266	0.0044
KL+1/V4	GG	0.2285	0.1454	0.0075
KL+2/V4	AG	0.1205	0.0537	0.0107
S1/V3	AT	0.1050	0.0537	0.0224
F1/V2	GC	0.0000	0.0133	0.0076
ST+4/V2	AC	0.5158	0.6009	0.0372
ST+7/V2	GC	0.7817	0.8578	0.0144
S1/V2	AC	0.1048	0.0536	0.0272
S1/V2	GC	0.8580	0.9308	0.0043
V-1/V2	AC	0.1105	0.0603	0.0307
V-1/V2	CC	0.8520	0.9237	0.0061
Q-1/V2	CC	0.8502	0.9122	0.0170
F1/V1	GA	0.0000	0.0116	0.0241
ST+7/V1	AA	0.1810	0.1226	0.0420
ST+7/V1	GA	0.7817	0.8578	0.0153
S1/V1	AA	0.1042	0.0536	0.0281
S1/V1	GA	0.8603	0.9271	0.0088
V-1/V1	AA	0.1111	0.0573	0.0190
V-1/V1	CA	0.8520	0.9237	0.0058
Q-1/V1	CA	0.8502	0.9122	0.0162
A-1/Q-1	AT	0.1435	0.0878	0.0350
D-1/Q-1	CC	0.4945	0.6157	0.0066
D-1/Q-1	CT	0.1302	0.0404	0.0018
D1/Q-1	TC	0.8502	0.9084	0.0288
D1/Q-1	TT	0.1498	0.0878	0.0224
F1/Q-1	GC	0.0000	0.0124	0.0499

**TABLE 21 (CON'T)**

Asthma Yes/No					
UK Population					
SNP	COMBINATION	HAPLOTYPE	FREQUENCIES		P-VALUE
			CNTL	CASE	
A-1/F+1	AA		0.3566	0.2591	0.0326
D1/F+1	TA		0.3594	0.2582	0.0243
D1/F+1	TG		0.6406	0.7370	0.0299
F+1/G-1	AT		0.2593	0.1505	0.0067
F+1/G-1	GT		0.6416	0.7475	0.0169
KL+2/M+1	AG		0.2845	0.2089	0.0491
KL+2/M+1	CG		0.5863	0.7094	0.0044
KL+2/L-1	AG		0.2845	0.2089	0.0463
KL+2/L-1	CG		0.5886	0.7083	0.0038
F+1/L-2	AG		0.2825	0.1781	0.0113
F+1/L-2	GG		0.6453	0.7449	0.0265
KL+2/L1	AC		0.2842	0.2039	0.0364
KL+2/L1	CC		0.7087	0.7913	0.0341
KL+2/L1	AT		0.0000	0.0048	0.0013
A-1/ST+4	AC		0.5160	0.4079	0.0279
D-1/ST+4	CA		0.3518	0.5012	0.0036
D-1/ST+4	CC		0.2594	0.1556	0.0097
D1/ST+4	TA		0.4805	0.5874	0.0297
D1/ST+4	TC		0.5195	0.4078	0.0243
F+1/ST+4	GA		0.2879	0.4771	<b>0.0002</b>
I1/ST+4	GA		0.3783	0.5243	0.0048
M+1/ST+4	GA		0.3805	0.5102	0.0104
L-1/ST+4	GA		0.3817	0.5088	0.0099
L-2/ST+4	GA		0.4814	0.5927	0.0201
L-2/ST+4	GC		0.4456	0.3304	0.0115
L1/ST+4	CA		0.4730	0.5923	0.0164
L1/ST+4	CC		0.5199	0.4029	0.0154
S+1/ST+4	TA		0.3623	0.4892	0.0096
S+1/ST+4	TC		0.1076	0.0166	<b>0.0002</b>
S1/ST+4	AA		0.1004	0.0481	0.0469
S1/ST+4	GA		0.3869	0.5440	<b>0.0005</b>
S1/ST+4	GC		0.5062	0.4080	0.0478
S2/ST+4	GA		0.2839	0.4669	<b>0.0001</b>
Q-1/ST+4	CA		0.3894	0.5556	<b>0.0006</b>
Q-1/ST+4	TA		0.0933	0.0367	0.0349
Q-1/ST+4	CC		0.4713	0.3675	0.0275
KL+2/ST+4	CA		0.3767	0.5474	<b>0.0008</b>
KL+2/ST+4	CC		0.3392	0.2451	0.0321
F+1/ST+5	AT		0.1239	0.0516	0.0325
F+1/ST+5	GT		0.3209	0.4485	0.0084
ST+4/ST+5	AT		0.3673	0.4973	0.0075

ST+4/ST+5	CT	0.0745	0.0053	<b>0.0002</b>
S1/ST+5	AT	0.1060	0.0481	0.0194
S1/ST+5	GT	0.3389	0.4514	0.0162
S2/ST+5	CT	0.1158	0.0535	0.0441
S2/ST+5	GT	0.3280	0.4471	0.0146
Q-1/ST+5	CT	0.3321	0.4553	0.0091
Q-1/ST+5	TT	0.1116	0.0446	0.0130
KL+2/ST+5	AT	0.1371	0.0486	0.0112
KL+2/ST+5	CT	0.3069	0.4528	0.0026
A-1/ST+6	AC	0.9889	0.9566	0.0352
A-1/ST+6	AT	0.0000	0.0097	0.0420
F+1/ST+6	AC	0.3594	0.2558	0.0219
F+1/ST+6	GC	0.6406	0.7345	0.0379
ST+4/ST+6	AC	0.4805	0.5824	0.0315
ST+4/ST+6	CC	0.5195	0.4078	0.0200
S1/ST+6	AC	0.1061	0.0435	0.0141
S1/ST+6	GC	0.8939	0.9468	0.0448
S2/ST+6	CC	0.2714	0.1563	0.0024
S2/ST+6	GC	0.7286	0.8339	0.0059
Q-1/ST+6	TC	0.1393	0.0725	0.0275
KL+2/ST+6	AC	0.2842	0.2057	0.0441
A-1/ST+7	TG	0.0050	0.0337	0.0331
D-1/ST+7	CA	0.1215	0.0403	0.0079
D-1/ST+7	CG	0.4896	0.6163	0.0109
F+1/ST+7	GG	0.6436	0.7514	0.0136
M+1/ST+7	GA	0.2044	0.1357	0.0478
M+1/ST+7	TA	0.0000	0.0003	0.0318
M+1/ST+7	GG	0.6647	0.7825	0.0050
L-1/ST+7	AA	0.0000	0.0001	0.0141
L-1/ST+7	GG	0.6671	0.7814	0.0062
L-2/ST+7	GA	0.1374	0.0583	0.0049
L-2/ST+7	GG	0.7911	0.8648	0.0346
ST+4/ST+7	AG	0.3873	0.5539	<b>0.0008</b>
ST+4/ST+7	CG	0.4077	0.3100	0.0358
ST+5/ST+7	TA	0.1173	0.0378	0.0063
ST+5/ST+7	TG	0.3264	0.4616	0.0044
ST+6/ST+7	CA	0.2050	0.1320	0.0388
S+1/ST+7	TA	0.1356	0.0466	0.0053
S+1/ST+7	TG	0.3319	0.4491	0.0167
S2/ST+7	CA	0.1338	0.0612	0.0187
S2/ST+7	GG	0.6567	0.7646	0.0124
Q-1/ST+7	TA	0.1355	0.0601	0.0078
F+1/S+1	AT	0.1466	0.0594	0.0180
F+1/S+1	GT	0.3228	0.4347	0.0234
S1/S+1	AT	0.1061	0.0481	0.0228

S2/S+1	CT	0.1383	0.0594	0.0253
S2/S+1	GT	0.3307	0.4341	0.0361
Q-1/S+1	CT	0.3373	0.4446	0.0208
Q-1/S+1	TT	0.1295	0.0494	0.0050
KL+2/S+1	AT	0.1417	0.0455	0.0039
KL+2/S+1	CT	0.3269	0.4547	0.0105
A-1/S1	AA	0.0982	0.0481	0.0473
A-1/S1	TA	0.0107	0.0000	0.0233
A-1/S1	TG	0.0000	0.0337	0.0033
D-1/S1	CA	0.1069	0.0481	0.0213
D-1/S1	GA	0.0000	0.0000	0.0063
D-1/S1	CG	0.5058	0.6053	0.0326
D1/S1	TA	0.1061	0.0481	0.0281
D1/S1	TG	0.8939	0.9471	0.0439
F+1/S1	AA	0.1052	0.0481	0.0289
F+1/S1	GG	0.6393	0.7464	0.0134
I1/S1	GA	0.1059	0.0481	0.0272
I1/S1	GG	0.7308	0.8440	0.0035
M+1/S1	GA	0.1061	0.0477	0.0251
M+1/S1	GG	0.7632	0.8705	0.0041
L-1/S1	AA	0.0000	0.0003	0.0453
L-1/S1	GA	0.1061	0.0478	0.0246
L-1/S1	GG	0.7658	0.8697	0.0031
KL+2/S1	AA	0.1067	0.0481	0.0210
A-1/S2	AC	0.2661	0.1602	0.0054
A-1/S2	AG	0.7227	0.8061	0.0351
A-1/S2	TG	0.0058	0.0337	0.0430
D-1/S2	CC	0.1196	0.0437	0.0144
D-1/S2	CG	0.4913	0.6091	0.0175
D-2/S2	CC	0.2700	0.1602	0.0047
D-2/S2	CG	0.7228	0.8298	0.0062
D1/S2	TC	0.2714	0.1602	0.0042
D1/S2	TG	0.7286	0.8350	0.0048
F+1/S2	AC	0.2575	0.1527	0.0048
F+1/S2	GG	0.6159	0.7381	0.0055
F1/S2	AC	0.2500	0.1408	0.0035
F1/S2	AG	0.7286	0.8400	0.0034
G-1/S2	TC	0.2605	0.1453	0.0017
G-1/S2	TG	0.6414	0.7558	0.0070
I1/S2	GC	0.1127	0.0521	0.0196
I1/S2	GG	0.7245	0.8356	0.0042
M+1/S2	GC	0.1429	0.0777	0.0261
M+1/S2	GG	0.7286	0.8405	0.0029
L-1/S2	GC	0.1464	0.0806	0.0265
L-1/S2	GG	0.7286	0.8353	0.0060

L-2/S2	GC	0.2714	0.1603	0.0031
L-2/S2	GG	0.6550	0.7628	0.0086
L1/S2	CC	0.2714	0.1602	0.0037
L1/S2	CG	0.7214	0.8350	0.0032
S1/S2	AC	0.1056	0.0481	0.0258
S1/S2	GG	0.7286	0.8402	0.0037
Q-1/S2	TC	0.1393	0.0769	0.0430
Q-1/S2	CG	0.7286	0.8405	0.0048
KL+1/S2	GC	0.2429	0.1402	0.0061
KL+1/S2	GG	0.7286	0.8400	0.0039
KL+2/S2	AC	0.1220	0.0456	0.0150
KL+2/S2	CG	0.5661	0.6769	0.0145
ST+4/T+1	AC	0.3961	0.5021	0.0315
ST+4/T+1	CT	0.0449	0.0000	0.0160
ST+7/T+1	GC	0.6645	0.7748	0.0088
S1/T+1	AC	0.1068	0.0476	0.0248
S1/T+1	GC	0.7600	0.8629	0.0068
S2/T+1	CC	0.1539	0.0781	0.0142
S2/T+1	GC	0.7233	0.8348	0.0037
Q-1/T+1	CC	0.7277	0.8334	0.0064
Q-1/T+1	TC	0.1393	0.0769	0.0300
ST+4/T+2	AT	0.4805	0.5898	0.0213
ST+4/T+2	CT	0.3945	0.2852	0.0158
S1/T+2	AG	0.0000	0.0090	0.0094
S1/T+2	AT	0.1061	0.0391	0.0094
S2/T+2	CG	0.0000	0.0014	0.0367
S2/T+2	CT	0.2714	0.1590	0.0033
S2/T+2	GT	0.6036	0.7160	0.0086
Q-1/T+2	TG	0.0000	0.0219	<b>0.0001</b>
Q-1/T+2	CT	0.7357	0.8200	0.0286
Q-1/T+2	TT	0.1393	0.0550	0.0040
ST+4/T1	AT	0.3801	0.5053	0.0106
ST+7/T1	AC	0.0000	0.0000	0.0411
ST+7/T1	GT	0.6634	0.7774	0.0060
S1/T1	AT	0.1061	0.0480	0.0250
S1/T1	GT	0.7617	0.8654	0.0046
S2/T1	CT	0.1435	0.0781	0.0276
S2/T1	GT	0.7244	0.8353	0.0030
Q-1/T1	CT	0.7286	0.8365	0.0041
Q-1/T1	TT	0.1393	0.0769	0.0320
KL+2/T1	CT	0.5834	0.7045	0.0058
ST+4/T2	AC	0.4031	0.5091	0.0300
ST+4/T2	CT	0.0282	0.0000	0.0472
S2/T2	CC	0.1674	0.0802	0.0044
S2/T2	GC	0.7243	0.8405	0.0020

A-1/V-1	AA	0.1292	0.0625	0.0197
A-1/V-1	TC	0.0044	0.0337	0.0209
D-1/V-1	CA	0.1227	0.0408	0.0032
D-1/V-1	CC	0.4893	0.6139	0.0107
D-2/V-1	CA	0.1357	0.0625	0.0105
D-2/V-1	CC	0.8571	0.9276	0.0204
D1/V-1	TA	0.1357	0.0625	0.0112
D1/V-1	TC	0.8643	0.9327	0.0143
F+1/V-1	AA	0.1357	0.0625	0.0112
F+1/V-1	GC	0.6385	0.7478	0.0135
F1/V-1	AA	0.1143	0.0483	0.0152
F1/V-1	AC	0.8643	0.9323	0.0175
G-1/V-1	TA	0.1280	0.0625	0.0209
I1/V-1	GA	0.1152	0.0487	0.0165
I1/V-1	GC	0.7217	0.8436	0.0033
M+1/V-1	GA	0.1357	0.0625	0.0066
M+1/V-1	GC	0.7336	0.8558	0.0011
L-1/V-1	GA	0.1357	0.0625	0.0091
L-1/V-1	GC	0.7361	0.8549	0.0009
L-2/V-1	GA	0.1357	0.0625	0.0079
L-2/V-1	GC	0.7910	0.8606	0.0476
L1/V-1	CA	0.1357	0.0625	0.0099
L1/V-1	CC	0.8571	0.9327	0.0077
ST+4/V-1	AA	0.0951	0.0400	0.0412
ST+4/V-1	AC	0.3881	0.5522	0.0008
ST+5/V-1	TA	0.1126	0.0513	0.0222
ST+5/V-1	TC	0.3312	0.4483	0.0121
ST+6/V-1	CA	0.1357	0.0580	0.0068
ST+6/V-1	CC	0.8643	0.9323	0.0183
ST+7/V-1	AA	0.1357	0.0625	0.0076
S+1/V-1	TA	0.1308	0.0625	0.0142
S+1/V-1	TC	0.3360	0.4299	0.0427
S1/V-1	AA	0.1056	0.0481	0.0242
S1/V-1	GC	0.8643	0.9375	0.0080
S2/V-1	CA	0.1357	0.0625	0.0111
S2/V-1	GC	0.7286	0.8404	0.0033
T+1/V-1	CA	0.1357	0.0625	0.0082
T+1/V-1	CC	0.7313	0.8480	0.0031
T+2/V-1	GA	0.0000	0.0124	0.0011
T+2/V-1	TA	0.1357	0.0501	0.0028
T+2/V-1	TC	0.7393	0.8249	0.0252
T1/V-1	TA	0.1357	0.0625	0.0076
T1/V-1	TC	0.7321	0.8510	0.0011
T2/V-1	CA	0.1357	0.0625	0.0085
T2/V-1	CC	0.7595	0.8560	0.0109



V-2/V-1	CA	0.1357	0.0625	0.0078
V-3/V-1	GA	0.1357	0.0625	0.0076
V-4/V-1	CA	0.1357	0.0625	0.0081
Q-1/V-1	TA	0.1357	0.0625	0.0096
Q-1/V-1	CC	0.8607	0.9231	0.0327
KL+1/V-1	GA	0.1071	0.0471	0.0157
KL+1/V-1	GC	0.8643	0.9322	0.0185
F+1/V-2	AC	0.2594	0.1241	0.0016
F+1/V-2	GC	0.3646	0.4832	0.0147
ST+4/V-2	AC	0.4811	0.5912	0.0214
ST+4/V-2	CC	0.1352	0.0194	<b>0.000003</b>
ST+7/V-2	AC	0.1518	0.0468	<b>0.0007</b>
S2/V-2	CC	0.2602	0.1415	0.0026
S2/V-2	GC	0.3611	0.4648	0.0271
Q-1/V-2	TC	0.1333	0.0500	0.0047
KL+2/V-2	AC	0.1372	0.0452	0.0032
F+1/V-3	AG	0.2594	0.1198	0.0017
F+1/V-3	GG	0.3604	0.4779	0.0188
ST+4/V-3	AG	0.4846	0.5861	0.0337
ST+4/V-3	CG	0.1352	0.0195	<b>0.000002</b>
ST+7/V-3	AG	0.1448	0.0422	0.0017
S2/V-3	CG	0.2656	0.1393	0.0018
S2/V-3	GG	0.3552	0.4609	0.0253
Q-1/V-3	TG	0.1332	0.0464	0.0031
KL+2/V-3	AG	0.1334	0.0402	0.0025
F+1/V-4	AC	0.2730	0.1336	0.0013
F+1/V-4	GC	0.4752	0.5994	0.0134
ST+4/V-4	AC	0.4830	0.5888	0.0283
ST+4/V-4	CC	0.2670	0.1405	<b>0.0006</b>
S2/V-4	CC	0.2635	0.1608	0.0116
ST+4/V7	AC	0.2894	0.4602	<b>&lt;0.0001</b>
ST+5/V7	TC	0.3313	0.4526	0.0101
ST+5/V7	TG	0.1135	0.0475	0.0319
ST+6/V7	CG	0.3417	0.2551	0.0459
S1/V7	GC	0.6588	0.7437	0.0491
S1/V7	AG	0.1044	0.0481	0.0265
S2/V7	GC	0.6442	0.7297	0.0480
S2/V7	CG	0.2557	0.1424	0.0025
V-1/V7	CC	0.6543	0.7440	0.0373
V-1/V7	AG	0.1311	0.0625	0.0160
V-2/V7	CC	0.3626	0.4677	0.0309
V-2/V7	CG	0.2615	0.1394	0.0032
V-3/V7	GC	0.3577	0.4643	0.0319
V-3/V7	GG	0.2625	0.1332	0.0041
V-4/V7	CC	0.4828	0.5823	0.0361

V-4/V7	CG	0.2654	0.1492	0.0049
V6/V7	CC	0.6587	0.7449	0.0458
V6/V7	CG	0.2583	0.1589	0.0077
V4/V7	GG	0.1376	0.0481	0.0100
F+1/V6	AC	0.2728	0.1677	0.0085
F+1/V6	GC	0.6434	0.7361	0.0366
S2/V6	CC	0.2630	0.1341	<b>0.0008</b>
S2/V6	GC	0.6543	0.7697	0.0067
V-1/V6	AC	0.1357	0.0625	0.0070
S1/V5	AA	0.1052	0.0481	0.0272
S1/V5	GA	0.8662	0.9374	0.0134
S2/V5	CA	0.2429	0.1457	0.0096
S2/V5	GA	0.7286	0.8399	0.0030
V-1/V5	AA	0.1071	0.0481	0.0170
V-1/V5	CA	0.8643	0.9375	0.0092
V4/V5	CA	0.7322	0.8365	0.0058
V4/V5	GA	0.2392	0.1490	0.0125
A-1/V4	AG	0.2406	0.1598	0.0286
D-1/V4	CC	0.4933	0.6166	0.0129
D-1/V4	CG	0.1175	0.0436	0.0104
D1/V4	TC	0.7536	0.8317	0.0347
D1/V4	TG	0.2464	0.1635	0.0282
F+1/V4	GC	0.5378	0.6500	0.0227
F+1/V4	AG	0.1461	0.0698	0.0294
F1/V4	AC	0.7357	0.8305	0.0142
F1/V4	AG	0.2429	0.1501	0.0113
I1/V4	GC	0.6087	0.7379	0.0052
M+1/V4	GC	0.6313	0.7548	0.0033
M+1/V4	GG	0.2378	0.1635	0.0415
L-1/V4	GC	0.6336	0.7539	0.0045
L-1/V4	GG	0.2385	0.1635	0.0418
ST+4/V4	AC	0.3687	0.5492	<b>0.0004</b>
ST+4/V4	CC	0.3849	0.2874	0.0370
ST+4/V4	AG	0.1112	0.0437	0.0280
ST+5/V4	TC	0.3273	0.4535	0.0111
ST+5/V4	TG	0.1163	0.0473	0.0218
ST+6/V4	CC	0.7536	0.8305	0.0404
ST+6/V4	CG	0.2464	0.1598	0.0231
S2/V4	GC	0.6128	0.7342	0.0046
S2/V4	CG	0.1307	0.0575	0.0224
T+1/V4	CC	0.6337	0.7460	0.0108
T+2/V4	TG	0.1299	0.0588	0.0148
T1/V4	TC	0.6314	0.7500	0.0060
T1/V4	TG	0.2365	0.1635	0.0487
V-1/V4	CC	0.7287	0.8312	0.0058

V-1/V4	AG	0.1109	0.0572	0.0487
V-3/V4	GG	0.1290	0.0465	0.0169
V3/V4	TC	0.5555	0.6792	0.0126
V3/V4	TG	0.2281	0.1218	0.0110
V2/V4	CC	0.7359	0.8365	0.0074
V2/V4	CG	0.2388	0.1536	0.0181
V1/V4	AC	0.7372	0.8365	0.0088
V1/V4	AG	0.2409	0.1490	0.0115
KL+2/V4	CC	0.5826	0.6791	0.0297
KL+2/V4	AG	0.1137	0.0511	0.0356
ST+4/V3	AT	0.4809	0.5922	0.0217
ST+4/V3	CT	0.3040	0.2114	0.0260
S1/V3	AT	0.1056	0.0481	0.0271
S2/V3	CT	0.2307	0.1339	0.0199
S2/V3	GT	0.5541	0.6669	0.0196
F+1/V2	AC	0.3349	0.2474	0.0471
F+1/V2	GC	0.6396	0.7428	0.0206
ST+4/V2	AC	0.4816	0.5923	0.0225
ST+4/V2	CC	0.4930	0.3977	0.0482
S1/V2	AC	0.1047	0.0481	0.0293
S1/V2	GC	0.8699	0.9421	0.0100
S2/V2	CC	0.2461	0.1502	0.0098
S2/V2	GC	0.7286	0.8399	0.0028
V-1/V2	AC	0.1100	0.0521	0.0265
V-1/V2	CC	0.8643	0.9375	0.0089
S2/V1	CA	0.2494	0.1457	0.0054
S2/V1	GA	0.7286	0.8399	0.0032
V-1/V1	AA	0.1131	0.0481	0.0127
V-1/V1	CA	0.8643	0.9375	0.0080
A-1/Q-1	TC	0.0044	0.0337	0.0204
D-1/Q-1	CC	0.4861	0.6205	0.0077
D-1/Q-1	CT	0.1258	0.0353	0.0017
D1/Q-1	TT	0.1393	0.0769	0.0437
F+1/Q-1	GC	0.6387	0.7449	0.0142
F+1/Q-1	AT	0.1393	0.0769	0.0410
I1/Q-1	GC	0.7216	0.8449	0.0040
I1/Q-1	GT	0.1153	0.0477	0.0175
M+1/Q-1	GC	0.7300	0.8413	0.0021
M+1/Q-1	GT	0.1393	0.0769	0.0334
L-1/Q-1	GC	0.7325	0.8405	0.0033
L-1/Q-1	GT	0.1393	0.0769	0.0314
A-1/KL+2	TC	0.0045	0.0337	0.0210
F+1/KL+2	GC	0.4735	0.6026	0.0137
I1/KL+2	GC	0.5614	0.6826	0.0071

**TABLE 21 (CON'T)**

Asthma Yes/No US Population				
SNP COMBINATION	HAPLOTYPE	FREQUENCIES		P-VALUE
		CNTL	CASE	
A-1/I1	AA	0.1208	0.2963	0.0025
A-1/I1	AG	0.8337	0.7037	0.0387
D-1/I1	GA	0.1281	0.2963	0.0039
D-2/I1	CA	0.1275	0.2963	0.0049
D-2/I1	CG	0.8658	0.7037	0.0065
D1/I1	TA	0.1284	0.2963	0.0037
D1/I1	TG	0.8716	0.7037	0.0037
F+1/I1	AA	0.1228	0.2963	0.0048
F1/I1	AA	0.0745	0.2222	0.0047
F1/I1	AG	0.8736	0.7037	0.0026
G-1/I1	TA	0.1280	0.2963	0.0054
A-1/M+1	AT	0.0773	0.2222	0.0072
D-1/M+1	GT	0.0705	0.2222	0.0066
D-2/M+1	CG	0.9138	0.7778	0.0134
D-2/M+1	CT	0.0795	0.2222	0.0072
D1/M+1	TG	0.9200	0.7778	0.0080
D1/M+1	TT	0.0800	0.2222	0.0080
F1/M+1	AG	0.8679	0.7037	0.0032
F1/M+1	AT	0.0801	0.2222	0.0058
G-1/M+1	TT	0.0720	0.2222	0.0052
I1/M+1	GG	0.8654	0.7037	0.0065
I1/M+1	AT	0.0729	0.2222	0.0047
L-1/M+1	GG	0.9200	0.7778	0.0081
L-1/M+1	AT	0.0800	0.2222	0.0064
L-2/M+1	GT	0.0795	0.2222	0.0060
L1/M+1	CG	0.9135	0.7778	0.0117
L1/M+1	CT	0.0800	0.2222	0.0075
KL+1/M+1	GG	0.8614	0.7194	0.0119
KL+1/M+1	GT	0.0801	0.2222	0.0052
KL+2/M+1	CG	0.6284	0.4667	0.0317
KL+2/M+1	CT	0.0794	0.2222	0.0057
A-1/L-1	AA	0.0773	0.2222	0.0045
D-1/L-1	GA	0.0705	0.2222	0.0036
D-2/L-1	CA	0.0795	0.2222	0.0051
D-2/L-1	CG	0.9138	0.7778	0.0127
D1/L-1	TA	0.0800	0.2222	0.0081
D1/L-1	TG	0.9200	0.7778	0.0081
F+1/L-1	AA	0.0742	0.2222	0.0059

F1/L-1	AA	0.0801	0.2222	0.0047
F1/L-1	AG	0.8679	0.7037	0.0028
G-1/L-1	TA	0.0720	0.2222	0.0034
I1/L-1	AA	0.0729	0.2222	0.0053
I1/L-1	GG	0.8654	0.7037	0.0057
L-2/L-1	GA	0.0795	0.2222	0.0053
KL+1/L-1	GA	0.0801	0.2222	0.0038
KL+1/L-1	GG	0.8614	0.7194	0.0131
KL+2/L-1	CA	0.0794	0.2222	0.0067
KL+2/L-1	CG	0.6284	0.4667	0.0317
I1/L-2	AG	0.1285	0.2963	0.0047
I1/L-2	GG	0.8048	0.6667	0.0293
I1/L1	AC	0.1284	0.2963	0.0050
I1/L1	GC	0.8651	0.7037	0.0064
L-1/L1	AC	0.0800	0.2222	0.0075
L-1/L1	GC	0.9135	0.7778	0.0130
I1/ST+4	AA	0.0925	0.2963	<b>0.0004</b>
M+1/ST+4	TA	0.0797	0.2222	0.0057
L-1/ST+4	AA	0.0797	0.2222	0.0072
S+1/ST+4	AA	0.0944	0.2795	0.0014
F1/ST+5	GT	0.0000	0.0741	0.0248
M+1/ST+5	TC	0.0800	0.2222	0.0141
L-1/ST+5	AC	0.0800	0.2222	0.0142
ST+4/ST+5	AC	0.0784	0.2483	0.0023
ST+4/ST+5	CT	0.0070	0.0572	0.0174
I1/ST+6	AC	0.1284	0.2963	0.0035
I1/ST+6	GC	0.8586	0.7037	0.0067
M+1/ST+6	GC	0.9070	0.7778	0.0132
M+1/ST+6	TC	0.0800	0.2222	0.0067
L-1/ST+6	AC	0.0800	0.2222	0.0059
L-1/ST+6	GC	0.9070	0.7778	0.0121
F+1/ST+7	AG	0.1008	0.2593	0.0066
I1/ST+7	AG	0.0765	0.2530	0.0090
M+1/ST+7	TG	0.0786	0.2222	0.0099
L-1/ST+7	AG	0.0786	0.2222	0.0090
M+1/S+1	TA	0.0801	0.2222	0.0127
L-1/S+1	AA	0.0801	0.2222	0.0119
S2/S+1	CA	0.0376	0.2323	0.0031
I1/S1	AG	0.1271	0.2871	0.0044
F1/S2	AG	0.7532	0.6026	0.0483
I1/S2	AC	0.1302	0.2561	0.0307
I1/S2	GG	0.7532	0.6080	0.0435
M+1/S2	TC	0.0823	0.2222	0.0101
Q-1/S2	CC	0.0779	0.2222	0.0072
A-1/T+1	AT	0.0771	0.2000	0.0178

D-1/T+1	GT	0.0572	0.2034	0.0064
D-2/T+1	CC	0.9136	0.8000	0.0254
D-2/T+1	CT	0.0798	0.2000	0.0219
D1/T+1	TC	0.9203	0.8000	0.0259
D1/T+1	TT	0.0797	0.2000	0.0229
I1/T+1	GC	0.8511	0.6828	0.0051
I1/T+1	AT	0.0638	0.2029	0.0059
M+1/T+1	GC	0.9078	0.7588	0.0080
M+1/T+1	TT	0.0779	0.2222	0.0046
L-1/T+1	GC	0.9078	0.7588	0.0092
L-1/T+1	AT	0.0779	0.2222	0.0062
L1/T+1	CC	0.9137	0.8000	0.0291
L1/T+1	CT	0.0798	0.2000	0.0232
T1/T+1	TC	0.9078	0.7407	0.0040
T1/T+1	CT	0.0779	0.2407	0.0028
T2/T+1	CC	0.9077	0.7584	0.0077
T2/T+1	TT	0.0768	0.2037	0.0154
I1/T+2	AT	0.1290	0.2963	0.0042
M+1/T+2	TT	0.0802	0.2198	0.0080
L-1/T+2	AT	0.0802	0.2198	0.0073
T1/T+2	CT	0.0779	0.2407	0.0042
T2/T+2	TT	0.0747	0.1986	0.0153
A-1/T1	AC	0.0751	0.2407	0.0025
A-1/T1	AT	0.8795	0.7593	0.0440
D-1/T1	GC	0.0678	0.2069	0.0076
D-2/T1	CC	0.0779	0.2407	0.0049
D-2/T1	CT	0.9154	0.7593	0.0051
D1/T1	TC	0.0779	0.2407	0.0052
D1/T1	TT	0.9221	0.7593	0.0052
F+1/T1	AC	0.0677	0.2189	0.0030
F1/T1	AC	0.0779	0.2407	0.0040
F1/T1	AT	0.8701	0.6852	0.0039
G-1/T1	TC	0.0699	0.2407	0.0012
I1/T1	AC	0.0710	0.2210	0.0054
I1/T1	GT	0.8674	0.6839	0.0033
M+1/T1	TC	0.0779	0.2222	0.0068
M+1/T1	GT	0.9221	0.7593	0.0045
L-1/T1	AC	0.0779	0.2222	0.0055
L-1/T1	GT	0.9221	0.7593	0.0033
L-2/T1	GC	0.0774	0.2407	0.0024
L-2/T1	GT	0.8558	0.7222	0.0350
L1/T1	CC	0.0779	0.2407	0.0039
L1/T1	CT	0.9156	0.7593	0.0064
ST+4/T1	AC	0.0779	0.2407	0.0032
ST+5/T1	CC	0.0779	0.2134	0.0126

ST+6/T1	CC	0.0779	0.2407	0.0038
ST+6/T1	CT	0.9091	0.7593	0.0059
ST+7/T1	GC	0.0779	0.2407	0.0026
S+1/T1	AC	0.0779	0.2098	0.0138
S1/T1	GC	0.0779	0.2222	0.0071
S2/T1	CC	0.0779	0.2205	0.0051
Q-1/T1	CC	0.0779	0.2407	0.0041
KL+1/T1	GC	0.0779	0.2407	0.0041
KL+1/T1	GT	0.8636	0.7009	0.0072
KL+2/T1	CC	0.0779	0.2407	0.0035
KL+2/T1	CT	0.6299	0.4478	0.0201
A-1/T2	AT	0.0713	0.2037	0.0099
D-1/T2	GT	0.0629	0.2037	0.0059
D-2/T2	CC	0.9190	0.7963	0.0225
D-2/T2	CT	0.0743	0.2037	0.0133
D1/T2	TC	0.9257	0.7963	0.0154
D1/T2	TT	0.0743	0.2037	0.0154
G-1/T2	TT	0.0657	0.2037	0.0079
I1/T2	GC	0.8670	0.7037	0.0072
I1/T2	AT	0.0680	0.2037	0.0093
M+1/T2	GC	0.9221	0.7778	0.0046
M+1/T2	TT	0.0779	0.2037	0.0112
L-1/T2	GC	0.9221	0.7778	0.0053
L-1/T2	AT	0.0779	0.2037	0.0127
L1/T2	CC	0.9192	0.7963	0.0216
L1/T2	CT	0.0743	0.2037	0.0128
ST+6/T2	CC	0.9126	0.7963	0.0233
ST+6/T2	CT	0.0744	0.2037	0.0109
ST+7/T2	GT	0.0743	0.2037	0.0126
T1/T2	TC	0.9221	0.7593	0.0027
T1/T2	CT	0.0779	0.2037	0.0105
KL+2/T2	CC	0.6343	0.4855	0.0424
KL+2/T2	CT	0.0735	0.2037	0.0101
I1/V-1	AC	0.0791	0.2412	0.0093
M+1/V-1	TC	0.0792	0.2222	0.0069
L-1/V-1	AC	0.0792	0.2222	0.0095
S2/V-1	CC	0.0779	0.2222	0.0078
T1/V-1	CC	0.0779	0.2407	0.0034
I1/V-2	AC	0.1272	0.2963	0.0020
M+1/V-2	TC	0.0795	0.2222	0.0074
L-1/V-2	AC	0.0795	0.2222	0.0084
T1/V-2	CC	0.0779	0.2407	0.0025
I1/V-3	AG	0.1272	0.2963	0.0033
M+1/V-3	TG	0.0795	0.2222	0.0058
L-1/V-3	AG	0.0795	0.2222	0.0060

T1/V-3	CG	0.0779	0.2407	0.0033
I1/V-4	AC	0.1266	0.2963	0.0029
I1/V-4	GC	0.6427	0.4259	0.0031
M+1/V-4	GC	0.6902	0.5000	0.0057
M+1/V-4	TC	0.0793	0.2222	0.0054
L-1/V-4	AC	0.0793	0.2222	0.0058
L-1/V-4	GC	0.6902	0.5000	0.0071
T+1/V-4	CC	0.6995	0.5159	0.0132
T+1/V-4	TC	0.0701	0.2063	0.0078
T1/V-4	CC	0.0779	0.2407	0.0028
T1/V-4	TC	0.6916	0.4815	0.0053
T2/V-4	CC	0.6955	0.5185	0.0159
T2/V-4	TC	0.0743	0.2037	0.0118
I1/V7	AG	0.1341	0.2544	0.0489
M+1/V7	TG	0.0848	0.2222	0.0106
L-1/V7	AG	0.0848	0.2222	0.0104
T1/V7	CG	0.0779	0.2198	0.0068
V4/V7	GC	0.1042	0.0000	0.0223
M+1/V6	TT	0.0000	0.0492	0.0328
L-1/V6	AT	0.0000	0.0492	0.0321
ST+4/V6	AT	0.0000	0.0668	0.0303
ST+7/V6	GT	0.0000	0.0600	0.0158
T1/V6	CC	0.0779	0.1883	0.0237
T1/V6	CT	0.0000	0.0525	0.0210
T2/V6	TT	0.0000	0.0501	0.0274
I1/V5	AA	0.0897	0.2765	0.0010
I1/V5	GA	0.8579	0.7037	0.0095
M+1/V5	TA	0.0801	0.2222	0.0073
L-1/V5	AA	0.0801	0.2222	0.0068
T1/V5	CA	0.0779	0.2407	0.0043
T1/V5	TA	0.8686	0.7398	0.0248
T2/V5	TA	0.0745	0.2037	0.0112
F+1/V4	GG	0.1061	0.0000	0.0208
I1/V4	AG	0.0000	0.0645	0.0242
M+1/V4	TC	0.0786	0.2222	0.0090
L-1/V4	AC	0.0786	0.2222	0.0096
L-2/V4	AG	0.0000	0.0370	0.0297
ST+7/V4	AC	0.1396	0.0188	0.0120
ST+7/V4	GC	0.6526	0.8145	0.0190
ST+7/V4	GG	0.1049	0.0188	0.0362
T1/V4	CC	0.0779	0.2407	0.0034
V-1/V4	AC	0.0728	0.0000	0.0279
V1/V4	TC	0.0594	0.0000	0.0483
Q-1/V4	TC	0.0715	0.0000	0.0322
I1/V3	AT	0.0903	0.2963	0.0009



I1/V3	GT	0.6759	0.4259	0.0016
M+1/V3	GT	0.6863	0.5000	0.0068
M+1/V3	TT	0.0800	0.2222	0.0053
L-1/V3	AT	0.0800	0.2222	0.0048
L-1/V3	GT	0.6863	0.5000	0.0033
T+1/V3	CT	0.6939	0.5159	0.0067
T+1/V3	TT	0.0723	0.2063	0.0087
T1/V3	CT	0.0779	0.2407	0.0036
T1/V3	TT	0.6883	0.4815	0.0023
T2/V3	CT	0.6923	0.5185	0.0132
T2/V3	TT	0.0739	0.2037	0.0097
I1/V2	AC	0.0752	0.2593	<b>0.0009</b>
I1/V2	GC	0.8664	0.7037	0.0065
M+1/V2	GC	0.8614	0.7407	0.0391
M+1/V2	TC	0.0801	0.2222	0.0078
L-1/V2	AC	0.0801	0.2222	0.0069
L-1/V2	GC	0.8614	0.7407	0.0390
T1/V2	CC	0.0779	0.2407	0.0056
T1/V2	TC	0.8636	0.7222	0.0252
I1/V1	AA	0.0750	0.2593	<b>0.0006</b>
I1/V1	GA	0.8648	0.7037	0.0075
M+1/V1	GA	0.8591	0.7407	0.0457
M+1/V1	TA	0.0800	0.2222	0.0070
L-1/V1	AA	0.0800	0.2222	0.0090
L-1/V1	GA	0.8591	0.7407	0.0486
T1/V1	CA	0.0779	0.2407	0.0042
T1/V1	TA	0.8611	0.7222	0.0223
I1/Q-1	AC	0.0788	0.2412	0.0094
M+1/Q-1	TC	0.0792	0.2222	0.0063
L-1/Q-1	AC	0.0792	0.2222	0.0072
I1/KL+1	AG	0.0752	0.2370	0.0024
I1/KL+1	GG	0.8664	0.7037	0.0060
I1/KL+2	AC	0.1269	0.2963	0.0032
I1/KL+2	GC	0.5809	0.3994	0.0091

**TABLE 22**

Haplotypes for 15-SNP Combination D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7	Freq_Control	Freq_Case (Asthma)	Pval-2sided
Combined US & UK			
CAGCGGTCACCTCACC	0.0000	0.0038	0.379
TAACACTCACTGACG	0.0016	0.0000	0.759
TAACGCCCACTCACC	0.0075	0.0076	0.968
TAACGCCCACTGACC	0.0023	0.0000	0.731
TAACGCCTACCCACG	0.0000	0.0000	0.542
TAACGCCTACTCACC	0.0830	0.0800	0.915
TAACGCCTACTCATG	0.0049	0.0192	0.130
TAACGCCTACTGACG	0.0082	0.0000	0.246
TAACGCTCACCCACC	0.0023	0.0046	0.642
TAACGCTCACCGACC	0.0000	0.0069	<b>0.048</b>
TAACGCTCTTCGGCG	0.0046	0.0000	0.518
TAACGGTCACCCACG	0.0000	0.0042	0.055
TAACGGTCACCTCACC	0.0032	0.0000	0.765
TAGCACTCACTCACC	0.0023	0.0000	0.723
TAGCACTCACTCACC	0.0026	0.0040	0.984
TAGCACTCACTGACG	0.0971	0.0532	<b>0.046</b>
TAGCGCCTACTCACC	0.0025	0.0000	0.657
TAGCGCCTACTCATG	0.0022	0.0000	0.864
TAGCGCTCACTCACC	0.0029	0.0000	0.353
TAGCGCTCACTCATG	0.0002	0.0000	0.842
TAGCGCTCACTGACC	0.0029	0.0000	0.501
TAGCGCTCACTGACG	0.0009	0.0000	0.972
TAGCGCTCACTGATG	0.0000	0.0000	0.383
TAGCGCTCTTCCGCG	0.0023	0.0000	1.000
TAGCGGCCACTCACC	0.0000	0.0038	0.377
TAGCGGCCACTCATC	0.0000	0.0038	0.401
TAGCGGCTACTGATG	0.0023	0.0000	0.998
TAGCGGTCACCCAACC	0.1762	0.1534	0.473
TAGCGGTCACCCATG	0.0000	0.0079	0.051
TAGCGGTCACCGACG	0.0065	0.0073	0.898
TAGCGGTCACTCACC	0.3648	0.4558	<b>0.025</b>
TAGCGGTCACTCACC	0.0024	0.0079	0.527
TAGCGGTCACTCATG	0.0707	0.0645	0.771
TAGCGGTCACTCGCC	0.0023	0.0000	0.462
TAGCGGTCACTGACC	0.0993	0.0777	0.393
TAGCGGTCACTGACG	0.0027	0.0000	0.918
TAGTGGTCACCCACC	0.0000	0.0038	0.133
TAGTGGTCACTCACC	0.0063	0.0000	0.451
TAGTGGTCACTGACC	0.0006	0.0000	0.838
TGACGCCTACTCACC	0.0000	0.0038	0.389
TGACGCTCTTCCACG	0.0032	0.0000	0.399
TGACGCTCTTCCGCC	0.0026	0.0000	0.681
TGACGCTCTTCCGCG	0.0169	0.0000	0.068

TGACGCTCTTCCGTG	0.0059	0.0000	0.369
TGACGCTCTTCGACG	0.0014	0.0000	0.956
TGACGCTCTTCGGCG	0.0023	0.0191	<b>0.026</b>
TGACGGTCACCCACC	0.0000	0.0076	0.127
Overall Test			0.052

**TABLE 22 (CON'T)**

Haplotypes for 15-SNP Combination D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7	Freq_Control	Freq_Case Asthma	Pval-2sided
UK			
CAGCGGTCACTCACC	0.00000	0.00481	0.439
TAACACTCACTGACG	0.00220	0.00000	0.856
TAACGCCCCACTCACG	0.01154	0.00481	0.442
TAACGCCCCACTGACC	0.00357	0.00000	0.999
TAACGCCTACCCACG	0.00000	0.01035	0.352
TAACGCCTACTCACG	0.08954	0.04715	0.146
TAACGCCTACTCATG	0.00709	0.01461	0.519
TAACGCCTACTGACG	0.01321	0.00000	0.162
TAACGCTCACCCACC	0.00357	0.00576	0.635
TAACGCTCACCGACC	0.00000	0.00867	0.060
TAACGCTCTTCGGCG	0.00714	0.00000	0.512
TAACGGTCACCCACC	0.00000	0.00000	0.642
TAACGGTCACCCACG	0.00000	0.00522	0.072
TAACGGTCACTCACC	0.00505	0.00000	0.603
TAGCACTCACTCACG	0.00412	0.00511	0.974
TAGCACTCACTGACG	0.09716	0.04297	<b>0.033</b>
TAGCGCCTACTCATG	0.00362	0.00000	0.834
TAGCGCTCACTGACC	0.00439	0.00000	0.554
TAGCGCTCACTGACG	0.00285	0.00000	0.815
TAGCGCTCACTGATG	0.00001	0.00000	0.487
TAGCGGCCACTCACG	0.00000	0.00481	0.422
TAGCGGCTACTCATG	0.00357	0.00000	1.000
TAGCGGTCACCCACC	0.18077	0.12795	0.168
TAGCGGTCACCCATG	0.00000	0.00527	0.271
TAGCGGTCACCGACC	0.00000	0.00497	0.154
TAGCGGTCACCGACG	0.00617	0.00910	0.798
TAGCGGTCACTCACC	0.35686	0.50471	<b>0.003</b>
TAGCGGTCACTCACG	0.00000	0.01009	<b>0.050</b>
TAGCGGTCACTCATG	0.06867	0.07627	0.765
TAGCGGTCACTGACC	0.09579	0.08333	0.674
TAGCGGTCACTGACG	0.00454	0.00000	0.895
TAGTGGTCACCCACC	0.00000	0.00481	0.216
TAGTGGTCACTCACC	0.00488	0.00000	0.637
TAGTGGTCACTGACC	0.00226	0.00000	0.731
TGACGCCTACTCACG	0.00000	0.00481	0.426

TGACGCTCTTCCGCC	0.00357	0.00000	1.000
TGACGCTCTTCCGCG	0.01429	0.00000	0.183
TGACGCTCTTCGGCG	0.00357	0.01442	0.259
Overall Test			0.061

**TABLE 22 (CON'T)**

Haplotypes for 15-SNP Combination D1/F1/1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7	Freq_Control	Freq_Case Asthma	Pval-2sided
US			
TAACGCCCACTCACG	0.00000	0.01852	0.239
TAACGCCTACTCACG	0.07143	0.14815	0.113
TAACGCCTACTCATG	0.00000	0.03704	<b>0.025</b>
TAACGCCTACTGACG	0.00000	0.01852	0.058
TAACGGTCACCGACG	0.00003	0.00000	0.858
TAACGGTCTCCGACG	0.00003	0.00000	0.858
TAGCACTCACTCACC	0.00653	0.00000	0.351
TAGCACTCACTGACG	0.09737	0.09259	0.986
TAGCGCTACTCACG	0.00649	0.00000	0.999
TAGCGCTCACTCACG	0.00539	0.00000	0.466
TAGCGCTCACTCATG	0.00052	0.00000	0.836
TAGCGCTCACTCGCG	0.00035	0.00000	0.527
TAGCGCTCACTCGTG	0.00024	0.00000	0.568
TAGCGCTCTTCCGCG	0.00649	0.00000	0.991
TAGCGGCCACTCATC	0.00000	0.01852	0.257
TAGCGGTCACCCACC	0.16880	0.20370	0.612
TAGCGGTCACCGACG	0.00643	0.00000	0.148
TAGCGGTCACTCACC	0.38579	0.35185	0.690
TAGCGGTCACTCACG	0.00658	0.00000	0.788
TAGCGGTCACTCATG	0.07254	0.01852	0.197
TAGCGGTCACTCGCC	0.00682	0.00000	0.517
TAGCGGTCACTGACC	0.09970	0.00000	<b>0.044</b>
TAGCGGTCACTGATG	0.00000	0.01852	0.080
TAGCGGTCTCCGACG	0.00003	0.00000	0.858
TAGTGGTCACTCACC	0.00649	0.00000	1.000
TGACGCTCTTCCACG	0.00889	0.00000	0.285
TGACGCTCTTCCGCG	0.02049	0.00000	0.510
TGACGCTCTTCCGTG	0.01837	0.00000	0.478
TGACGCTCTTCGACG	0.00420	0.00000	0.839
TGACGCTCTTCGGCG	0.00000	0.03704	<b>0.022</b>
TGACGGTCACCCACC	0.00000	0.03704	0.067
Overall Test			<b>0.011</b>

TABLE  
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	A-1	D-2	D-1	D1	F1	F+1	G-1	I1	KL+1	KL+2	L-2	L-1
A-1	1	0.9529	0.9727	0.2876	0.9539	0.7964	0.9928	0.9431	0.8188	0.6712	0.8919	0.9927
D-2		1	0.9567	0.2165	0.9034	0.901	0.9928	0.8645	0.7512	0.746	0.8051	0.5997
D-1			0.9149	0.2925	0.8483	0.3054	0.8715	0.7015	0.7977	0.7187	0.8363	0.9456
D1				0.2294	0.2716	0.281	0.3307	0.2165	0.144	0.1686	0.215	0.334
F1					0.7752	0.8773	0.9668	0.8418	0.5252	0.8173	0.8079	0.9186
F+1						0.8234	0.7017	0.7429	0.7876	0.8423	0.7771	0.9644
G-1							1	0.8821	0.8013	0.7226	0.7562	0.9985
I1								0.8709	0.8084	0.7252	0.813	0.8966
KL+1									0.5874	0.6914	0.6992	0.7074
KL+2										0.4343	0.5272	0.6919
L-2											0.5661	0.9002
L-1												1
L1												
M+1												
Q-1												
S1												
S2												
S+1												
ST+4												
ST+5												
ST+6												
ST+7												
T1												
T2												
T+1												
T+2												
V-4												
V-3												
V-2												
V-1												
V1												
V2												
V3												
V4												
V5												
V6												
V7												
CNTL	97.6%	0.7%	37.6%	0.0%	96.8%	65.2%	9.3%	84.9%	96.1%	71.3%	7.1%	86.9%
CASE	97.7%	0.8%	38.3%	0.8%	97.6%	66.7%	9.5%	86.7%	97.6%	75.0%	8.6%	88.1%

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TABLE 23  
(CONT')

T-2	V-4	V-3	V-2	V-1	V1	V2	V3	V4	V5	V6	V7	
0.8482	0.89	0.9528	0.9512	0.3159	0.8771	0.845	0.9899	0.8623	0.484	0.9605	0.9776	A-1
0.979	0.8212	0.8434	0.8525	0.2765	0.7716	0.7714	0.9487	0.7299	0.6333	0.9357	0.9153	D-2
0.9916	0.9347	0.9133	0.9249	0.0564	0.8796	0.822	0.9884	0.1208	0.5692	0.971	0.8871	D-1
0.3034	0.1998	0.2275	0.2333	0.0576	0.1613	0.1776	0.3193	0.1375	0.2874	0.2874	0.2847	D1
0.6339	0.8064	0.8232	0.8661	0.2774	0.5331	0.4447	0.906	0.0184	0.5392	0.7327	0.8979	F1
0.9921	0.8236	0.6936	0.8946	0.4217	0.759	0.7453	0.6747	0.7614	0.6817	0.9033	0.9703	F+1
0.9983	0.0387	0.1868	0.1352	0.4244	0.898	0.8347	0.9647	0.875	0.5984	0.8615	0.9708	G-1
0.8783	0.7126	0.9764	0.9693	0.1603	0.8451	0.8127	0.9476	0.291	0.6124	0.8066	0.9431	I1
0.51	0.5432	0.6507	0.6716	0.4052	0.693	0.7103	0.7193	0.0214	0.6347	0.5759	0.7509	KL+1
0.6942	0.4599	0.2933	0.2628	0.3928	0.761	0.8655	0.6792	0.3607	0.3552	0.6632	0.8712	KL-2
0.9438	0.1653	0.337	0.3167	0.2183	0.7599	0.718	0.8725	0.6472	0.4957	0.6938	0.7443	L-2
0.9922	0.8489	0.9039	0.7918	0.1445	0.7935	0.7484	0.9841	0.8094	0.4813	0.9861	0.906	L-1
0.9894	0.4355	0.7976	0.8198	0.2764	0.7585	0.7776	0.3862	0.795	0.6265	0.9268	0.9282	L1
0.9393	0.8497	0.8915	0.8256	0.1134	0.727	0.6878	0.9331	0.7771	0.4349	0.9799	0.9401	M+1
0.0858	0.5022	0.3237	0.3254	0.1916	0.3722	0.3942	0.5145	0.0169	0.477	0.3731	0.5975	Q-1
0.2486	0.3487	0.3812	0.3895	0.2292	0.3687	0.3258	0.3367	0.5046	0.2261	0.1924	0.5646	S1
0.3579	0.5199	0.4154	0.6053	0.2705	0.3718	0.3781	0.4378	0.4948	0.456	0.6213	0.4937	S2
0.9862	0.5669	0.4733	0.5306	0.3477	0.908	0.8681	0.8838	0.7628	0.5922	0.9668	0.2078	S+1
0.3088	0.0376	0.0042	0.0038	0.139	0.353	0.333	0.3039	0.2464	0.3668	0.5261	0.3597	ST+4
0.9932	0.733	0.7512	0.8109	0.268	0.8394	0.7983	0.9371	0.6239	0.6703	0.9659	0.4647	ST+5
0.8479	0.5565	0.614	0.6481	0.2999	0.4789	0.438	0.8066	0.6202	0.2509	0.8978	0.8061	ST+6
0.4743	0.3208	0.1277	0.083	0.2411	0.5304	0.5132	0.5422	0.6648	0.5673	0.5416	0.5646	ST+7
0.9796	0.8138	0.879	0.581	0.189	0.8002	0.7617	0.994	0.7894	0.48	0.9979	0.9953	T1
0.9857	0.8496	0.909	0.6429	0.2331	0.78	0.7431	0.983	0.6718	0.4917	0.8255	0.9527	T2
0.8415	0.6299	0.6959	0.2654	0.1373	0.7815	0.7353	0.8371	0.7952	0.4621	0.7175	0.8549	T+1
1	0.9018	0.8474	0.8721	0.1511	0.5547	0.5013	0.869	0.7161	0.1961	0.9947	0.9285	T+2
.	0.5602	0.7545	0.7392	0.2846	0.7306	0.6778	0.6548	0.6956	0.4482	0.3053	0.7861	V-4
.	.	0.6016	0.5787	0.3009	0.723	0.6828	0.8121	0.7578	0.4812	0.4752	0.48	V-3
.	.	.	0.677	0.3168	0.7514	0.7246	0.8283	0.7598	0.5046	0.4345	0.5332	V-2
.	.	.	.	0.1413	0.2746	0.2721	0.3847	0.0213	0.3949	0.2771	0.3088	V-1
.	.	.	.	.	0.7758	0.3578	0.7508	0.0318	0.6882	0.6885	0.8552	V1
.	.	.	.	.	.	0.5856	0.7448	0.036	0.666	0.6535	0.814	V2
.	.	.	.	.	.	1	0.6569	0.6558	0.6352	0.6352	0.6352	V3
.	.	.	.	.	.	.	0.4009	0.0641	0.6776	0.8394	0.6776	V4
.	.	.	.	.	.	.	.	0.3878	0.4815	0.6514	0.6514	V5
.	.	.	.	.	.	.	.	.	0.8592	0.8756	0.8756	V6
.	.	.	.	.	.	.	.	.	.	0.8294	0.8294	V7
88.3%	24.4%	37.1%	36.8%	85.2%	96.5%	96.5%	77.8%	76.7%	96.3%	8.7%	66.5%	CNTL
88.3%	27.0%	39.7%	39.1%	90.6%	97.6%	97.7%	78.3%	80.5%	98.4%	9.4%	67.7%	CASE

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TABLE  
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	A-1	D-2	D-1	D1	F1	F+1	G-1	I1	KL+1	KL+2	L-2	L-1	L1
A-1	0.36	0.708	0.5366	0.2337	0.4821	0.2687	0.549	0.1166	0.5205	0.1167	0.4407	0.2073	0.712
D-2	.	1	0.9772	0.2541	0.9201	0.2648	0.9819	0.2427	0.8673	0.4335	0.8401	0.182	0.872
D-1	.	.	1	0.377	0.9873	0.1133	0.7887	0.1193	0.9308	0.3947	0.8289	0.2098	0.9961
D1	.	.	.	0.2646	0.3673	0.0669	0.3912	0.0339	0.2861	0.0734	0.2859	0.0602	0.3952
F1	.	.	.	.	1	0.2592	0.9556	0.1925	0.7427	0.411	0.9067	0.275	1
F+1	.	.	.	.	.	0.1466	0.2369	0.1765	0.2734	0.2218	0.1379	0.2587	0.3273
G-1	.	.	.	.	.	.	1	0.377	0.8883	0.372	0.862	0.3524	0.9593
I1	.	.	.	.	.	.	.	0.0952	0.1919	0.0537	0.2313	0.274	0.1586
KL+1	.	.	.	.	.	.	.	.	1	0.3614	0.7995	0.2412	0.8525
KL+2	.	.	.	.	.	.	.	.	.	0.186	0.2005	0.0601	0.101
L-2	.	.	.	.	.	.	.	.	.	.	0.6623	0.3081	0.8519
L-1	.	.	.	.	.	.	.	.	.	.	.	0.14	0.3011
L1	.	.	.	.	.	.	.	.	.	.	.	.	1
M+1	.	.	.	.	.	.	.	.	.	.	.	.	.
Q-1	.	.	.	.	.	.	.	.	.	.	.	.	.
S1	.	.	.	.	.	.	.	.	.	.	.	.	.
S2	.	.	.	.	.	.	.	.	.	.	.	.	.
S+1	.	.	.	.	.	.	.	.	.	.	.	.	.
ST+4	.	.	.	.	.	.	.	.	.	.	.	.	.
ST+5	.	.	.	.	.	.	.	.	.	.	.	.	.
ST+6	.	.	.	.	.	.	.	.	.	.	.	.	.
ST+7	.	.	.	.	.	.	.	.	.	.	.	.	.
T1	.	.	.	.	.	.	.	.	.	.	.	.	.
T2	.	.	.	.	.	.	.	.	.	.	.	.	.
T+1	.	.	.	.	.	.	.	.	.	.	.	.	.
T+2	.	.	.	.	.	.	.	.	.	.	.	.	.
V-4	.	.	.	.	.	.	.	.	.	.	.	.	.
V-3	.	.	.	.	.	.	.	.	.	.	.	.	.
V-2	.	.	.	.	.	.	.	.	.	.	.	.	.
V-1	.	.	.	.	.	.	.	.	.	.	.	.	.
V1	.	.	.	.	.	.	.	.	.	.	.	.	.
V2	.	.	.	.	.	.	.	.	.	.	.	.	.
V3	.	.	.	.	.	.	.	.	.	.	.	.	.
V4	.	.	.	.	.	.	.	.	.	.	.	.	.
V5	.	.	.	.	.	.	.	.	.	.	.	.	.
V6	.	.	.	.	.	.	.	.	.	.	.	.	.
V7	.	.	.	.	.	.	.	.	.	.	.	.	.
ONTL	98.9%	0.7%	38.9%	0.0%	97.9%	64.1%	9.9%	83.7%	97.1%	71.6%	7.3%	87.2%	0.7%
CASE	97.0%	1.0%	38.5%	1.0%	97.9%	73.3%	10.2%	91.0%	98.0%	79.0%	9.0%	93.0%	1.0%

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TABLE 24  
(CON'T)

T+2	V-4	V-3	V-2	V-1	V1	V2	V3	V4	V5	V6	V7
0.5378	0.5387	0.3985	0.4377	0.0358	0.4796	0.5546	0.5864	0.3556	0.5081	0.4864	0.3313 A-1
0.8364	0.9146	0.7946	0.8079	0.0986	0.899	0.8868	0.911	0.4377	0.8632	0.8983	0.3286 D-2
0.923	0.8625	0.6793	0.7517	0.0032	0.9844	0.9801	0.906	0.0795	0.9368	0.9516	0.2197 D-1
0.2632	0.3236	0.2098	0.2226	0.0261	0.3415	0.3127	0.3464	0.0805	0.2776	0.3444	0.0814 D1
0.6014	0.8456	0.8809	0.8894	0.0828	0.9054	0.6794	0.9407	0.1096	0.741	0.9323	0.4679 F1
0.5383	0.2015	0.0941	0.0889	0.0764	0.2653	0.2776	0.2953	0.2827	0.2736	0.1907	0.2765 F+1
0.9579	0.2008	0.5728	0.4178	0.199	0.977	0.9597	0.9943	0.5387	0.897	0.8895	0.4141 G-1
0.1879	0.2735	0.2945	0.3752	0.0131	0.1886	0.1953	0.2914	0.0776	0.1904	0.3067	0.3233 I1
0.5431	0.652	0.8099	0.8474	0.1057	0.4792	0.7282	0.9237	0.1425	0.7184	0.9339	0.471 KL+1
0.3258	0.1624	0.0295	0.0221	0.1072	0.4643	0.3616	0.3737	0.181	0.3531	0.2018	0.2549 KL+2
0.7347	0.412	0.6292	0.6143	0.1168	0.915	0.8836	0.8938	0.3978	0.7924	0.4923	0.132 L-2
0.3013	0.3228	0.3089	0.3945	0.0161	0.2758	0.2627	0.2798	0.1454	0.235	0.4755	0.2706 L-1
0.919	0.5609	0.8885	0.8959	0.1019	0.9108	0.9313	0.4078	0.5526	0.8573	0.9279	0.4095 L1
0.1593	0.1895	0.1689	0.2381	0.0027	0.1887	0.1546	0.1401	0.0703	0.1422	0.2664	0.2066 M+1
0.0061	0.2953	0.0965	0.1005	0.1087	0.1723	0.1642	0.3054	0.0777	0.1521	0.1824	0.2352 Q-1
0.029	0.1114	0.114	0.1165	0.1136	0.2175	0.1883	0.1067	0.1745	0.1552	0.0763	0.0969 S1
0.0046	0.0188	0.0117	0.0192	0.0128	0.0095	0.0085	0.0149	0.0301	0.0101	0.0284	0.024 S2
0.6635	0.3236	0.0551	0.069	0.0825	0.8858	0.8594	0.8424	0.338	0.8219	0.8633	0.094 S+1
0.2041	0.06	0.00168	0.00182	0.0318	0.335	0.323	0.2648	0.0776	0.3287	0.1976	0.0462 ST+4
0.5882	0.4927	0.139	0.2072	0.0195	0.819	0.7656	0.7317	0.1358	0.7821	0.7112	0.0613 ST+5
0.6532	0.8045	0.5219	0.5804	0.0392	0.8088	0.8121	0.8456	0.1998	0.7325	0.8153	0.1484 ST+6
0.3434	0.2081	0.0423	0.0213	0.0961	0.3538	0.3743	0.4358	0.2923	0.3845	0.0577	0.4097 ST+7
0.2624	0.2558	0.2507	0.2604	0.0148	0.2435	0.2306	0.2086	0.1162	0.2031	0.3843	0.2838 T1
0.3064	0.3544	0.3302	0.3068	0.0217	0.3049	0.2872	0.3118	0.0929	0.2748	0.2902	0.1935 T2
0.287	0.4368	0.4123	0.2166	0.018	0.3187	0.2775	0.334	0.154	0.2923	0.4282	0.2826 T+1
0.729	0.8668	0.821	0.8359	0.0142	0.5774	0.5592	0.6267	0.221	0.5078	0.8488	0.3249 T+2
	0.7889	0.8458	0.8917	0.114	0.8419	0.7436	0.4575	0.3953	0.6344	0.1679	0.2257 V-4
		0.5461	0.515	0.1121	0.8782	0.8174	0.849	0.3806	0.8083	0.294	0.0409 V-3
			0.5508	0.1127	0.9069	0.8391	0.8463	0.37	0.8381	0.2682	0.0479 V-2
				0.0454	0.0872	0.1019	0.2123	0.0725	0.1096	0.1137	0.1643 V-1
					1	0.72	0.9365	0.142	0.4753	0.9568	0.4768 V1
							0.1858	0.7287	0.9438	0.4826 V2	
							1	0.9552	0.1511	0.9776	0.2492 V3
									0.441	0.9013	0.2492 V3
									0.2122	0.1511	0.4256
										0.4256	0.2145 V4
										1	0.9366
											0.4654 V5
											0.1911 V6
											0.1635 V7
87.5%	25.2%	38.1%	37.6%	86.4%	97.8%	97.5%	78.5%	75.4%	97.1%	8.3%	65.8% CNTL
86.0%	26.5%	41.8%	41.0%	94.0%	98.0%	98.0%	79.4%	82.0%	98.0%	9.0%	74.0% CASE

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TABLE  
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	A-1	D-2	D-1	D1	F1	F+1	G-1	I1	KL+1	KL+2	L-2	L-1
A-1	0.5975	0.3497	0.5555	0.2976	0.6466	0.0791	0.4677	0.0672	0.5153	0.2438	0.423	0.0332
D-2	.	1	0.8165	0.4863	0.861	-0.0771	0.7403	0.1277	0.6542	0.3873	0.8502	0.0488
D-1	.	.	0.8204	0.803	0.7491	0.1511	0.9329	0.106	0.9195	0.488	0.9745	0.0446
D1	.	.	.	1	0.9107	0.0949	0.7353	0.0639	0.6944	0.3038	1	0.0475
F1	.	.	.	.	1	0.1077	0.9163	0.0575	0.9108	0.5115	0.9831	0.0728
F+1	.	.	.	.	.	0.051	0.1788	0.1392	0.1772	0.1169	0.125	0.0685
G-1	.	.	.	.	.	.	1	0.2194	0.7957	0.6347	0.8889	0.0883
I1	.	.	.	.	.	.	.	0.0455	0.1031	0.0248	0.2186	0.0886
KL+1	.	.	.	.	.	.	.	.	1	0.4925	0.9062	0.0616
KL+2	.	.	.	.	.	.	.	.	.	0.373	0.5852	0.011
L-2	.	.	.	.	.	.	.	.	.	.	1	0.085
L-1	.	.	.	.	.	.	.	.	.	.	.	0.0749
L1	.	.	.	.	.	.	.	.	.	.	.	.
M+1	.	.	.	.	.	.	.	.	.	.	.	.
Q-1	.	.	.	.	.	.	.	.	.	.	.	.
S1	.	.	.	.	.	.	.	.	.	.	.	.
S2	.	.	.	.	.	.	.	.	.	.	.	.
S+1	.	.	.	.	.	.	.	.	.	.	.	.
ST+4	.	.	.	.	.	.	.	.	.	.	.	.
ST+5	.	.	.	.	.	.	.	.	.	.	.	.
ST+6	.	.	.	.	.	.	.	.	.	.	.	.
ST+7	.	.	.	.	.	.	.	.	.	.	.	.
T1	.	.	.	.	.	.	.	.	.	.	.	.
T2	.	.	.	.	.	.	.	.	.	.	.	.
T+1	.	.	.	.	.	.	.	.	.	.	.	.
T+2	.	.	.	.	.	.	.	.	.	.	.	.
V-4	.	.	.	.	.	.	.	.	.	.	.	.
V-3	.	.	.	.	.	.	.	.	.	.	.	.
V-2	.	.	.	.	.	.	.	.	.	.	.	.
V-1	.	.	.	.	.	.	.	.	.	.	.	.
V1	.	.	.	.	.	.	.	.	.	.	.	.
V2	.	.	.	.	.	.	.	.	.	.	.	.
V3	.	.	.	.	.	.	.	.	.	.	.	.
V4	.	.	.	.	.	.	.	.	.	.	.	.
V5	.	.	.	.	.	.	.	.	.	.	.	.
V6	.	.	.	.	.	.	.	.	.	.	.	.
V7	.	.	.	.	.	.	.	.	.	.	.	.
CNTL	95.5%	0.7%	35.0%	0.0%	94.8%	67.4%	8.2%	87.2%	94.2%	70.8%	6.7%	92.0%
CASE	100.0%	0.0%	37.5%	0.0%	96.4%	46.4%	7.1%	71.4%	96.4%	60.7%	7.1%	75.0%

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TABLE 25  
(CON'T)

T+2	V-4	V-3	V-2	V-1	V1	V2	V3	V4	V5	V6	V7
0.218	0.3423	0.5529	0.5441	0.5101	0.4711	0.5151	0.5225	0.5089	0.1046	0.449	0.045 A-1
0.326	0.5949	0.804	0.8084	0.6979	0.5867	0.622	0.7337	0.6075	0.3122	0.8618	0.0681 D-2
0.3499	0.7362	0.7346	0.8037	0.9674	0.8785	0.9159	0.3423	0.9088	0.5057	0.9972	0.177 D-1
0.2831	0.6126	0.7618	0.7589	0.5318	0.5238	0.5204	0.9809	0.9808	0.2527	0.9355	0.0467 D1
0.4968	0.8032	0.9168	0.9379	0.6717	0.8313	0.9066	0.9029	0.1254	0.9782	0.843	0.0847 F1
0.1136	0.0543	0.2408	0.2587	0.2045	0.0721	0.0961	0.0939	0.0403	0.0484	0.1244	0.049 F+1
0.1269	0.596	0.6156	0.6151	0.7686	0.8235	0.8022	0.958	0.2096	0.3747	0.9724	0.1504 G-1
0.0962	0.0747	0.1537	0.1566	0.32	0.1047	0.1082	0.0662	0.0704	0.0436	0.1829	0.0916 I1
0.3822	0.819	0.8466	0.8566	0.7277	0.8564	0.9126	0.8304	0.1175	0.9779	0.8344	0.1605 KL+1
0.4833	0.8	0.6784	0.669	0.8194	0.6272	0.6266	0.3471	0.6488	0.2966	0.5418	0.1238 KL+2
0.1104	0.7716	0.7341	0.7371	0.7763	0.8287	0.9099	0.9976	0.126	0.4265	0.9523	0.0823 L-2
0.0616	0.03	0.0923	0.0885	0.0613	0.0733	0.0771	0.0617	0.0549	0.021	0.117	0.0612 L-1
0.3383	0.6666	0.8033	0.8012	0.7063	0.622	0.4986	0.9823	0.8172	0.3379	0.9969	0.0923 L1
0.0663	0.0362	0.0889	0.0908	0.0589	0.0728	0.0775	0.0587	0.0482	0.0205	0.1233	0.0569 M+1
0.4206	0.675	0.8774	0.8802	0.5321	0.4891	0.6443	0.827	0.1059	0.4645	0.9021	0.1941 Q-1
0.4388	0.579	0.7874	0.7907	0.169	0.7729	0.756	0.8052	0.471	0.3747	0.6597	0.2069 S1
0.0772	0.0191	0.0631	0.0586	0.0432	0.0272	0.0402	0.0809	0.159	0.0212	0.1053	0.1609 S2
0.1156	0.5745	0.2879	0.2918	0.4944	0.6326	0.6255	0.5402	0.4976	0.2757	0.4721	0.1374 S+1
0.4213	0.2581	0.7286	0.7176	0.8947	0.6902	0.7095	0.6102	0.8393	0.4613	0.3051	0.198 ST+4
0.1422	0.6944	0.397	0.4085	0.6082	0.3534	0.3751	0.6532	0.5451	0.2772	0.5542	0.1858 ST+5
0.3084	0.6626	0.8506	0.8528	0.6827	0.6204	0.7758	0.9984	0.6657	0.2924	0.9851	0.0466 ST+6
0.2091	0.9056	0.9296	0.9277	0.9212	0.5903	0.6683	0.8816	0.0196	0.4965	0.2486	0.0883 ST+7
0.0106	0.011	0.0344	0.0338	0.016	0.0174	0.0148	0.0135	0.0119	0.0077	0.0238	0.009 T1
0.1339	0.1063	0.1686	0.1703	0.1374	0.1403	0.1505	0.1143	0.1275	0.0459	0.1695	0.0871 T2
0.1305	0.0819	0.1712	0.1526	0.1187	0.1315	0.1362	0.1347	0.1037	0.0429	0.1655	0.1135 T+1
0.4778	0.4693	0.4677	0.4626	0.4513	0.3936	0.3756	0.5905	0.3994	0.1307	0.1602	0.1488 T+2
0.6296	0.3679	0.3736	0.6697	0.7697	0.7808	0.7839	0.905	0.6711	0.4172	0.9252	0.0491 V-4
0.8311	0.7505	0.8843	0.8229	0.8537	0.7839	0.5489	0.4291	0.9813	0.4291	0.9813	0.2166 V-3
0.8311	0.8311	0.8933	0.823	0.8502	0.823	0.8502	0.7853	0.5576	0.432	0.9786	0.2087 V-2
0.4964	0.5937	0.4964	0.6257	0.8256	0.1045	0.5162	0.9343	0.1855	0.9343	0.1855	0.0549 V1
0.5028	1	0.5028	1	0.5028	1	0.5028	0.7511	0.2124	0.9918	0.8038	0.0549 V1
0.8118	1	0.8118	1	0.8118	1	0.8118	0.985	0.8324	0.985	0.8324	0.0607 V2
0.6459	0.5315	0.6459	0.5315	0.6459	0.5315	0.6459	0.5315	0.6459	0.5315	0.6459	0.0773 V3
0.6206	0.3239	0.6206	0.3239	0.6206	0.3239	0.6206	0.3239	0.6206	0.3239	0.6206	0.0439 V4
0.4771	0.6065	0.4771	0.6065	0.4771	0.6065	0.4771	0.6065	0.4771	0.6065	0.4771	0.0353 V5
0.122	0.7369	0.122	0.7369	0.122	0.7369	0.122	0.7369	0.122	0.7369	0.122	0.0514 V7
89.6%	23.0%	35.3%	35.3%	82.9%	93.9%	94.2%	76.6%	79.2%	94.7%	9.5%	67.8% CNTL
96.4%	28.5%	32.1%	32.1%	78.6%	96.4%	96.4%	75.0%	75.0%	100.0%	10.7%	48.4% CASE

713411 v1

**TABLE 26**

BHR				
Combined US and UK				
SNP COMBINATION	HAPLOTYPE	FREQUENCIES		P-VALUE
		CNTL	CASE	
ST+4/ST+5	CT	0.0475	0.0000	0.0170
KL+2/ST+5	AT	0.1342	0.0261	0.0064
KL+2/ST+5	CT	0.3301	0.4441	0.0313
S+1/ST+7	TA	0.1504	0.0488	0.0083
KL+2/S+1	AT	0.1379	0.0253	0.0041
KL+2/S+1	CT	0.3500	0.4639	0.0373
ST+4/V-2	CC	0.1137	0.0241	<b>0.0022</b>
ST+4/V-3	CG	0.1118	0.0241	<b>0.0025</b>
G-1/V-4	CC	0.0387	0.0000	0.0389
ST+4/V-4	CC	0.2409	0.1345	0.0089
F1/V4	GG	0.0029	0.0234	0.0293
V-1/V4	AC	0.0423	0.0000	0.0191
Q-1/V4	TC	0.0446	0.0000	0.0218
D-1/Q-1	CT	0.1302	0.0168	0.0035
D-1/Q-1	GT	0.0196	0.0848	0.0096

**TABLE 26(CON'T)**

BHR				
UK Population				
SNP COMBINATION	HAPLOTYPE	FREQUENCIES		P-VALUE
		CNTL	CASE	
KL+2/M+1	CG	0.5863	0.7300	0.0129
KL+2/L-1	CG	0.5886	0.7284	0.0109
M+1/ST+4	GA	0.3805	0.5109	0.0368
L-1/ST+4	GA	0.3817	0.5087	0.0475
S+1/ST+4	TA	0.3623	0.5100	0.0195
S+1/ST+4	TC	0.1076	0.0225	0.0110
S1/ST+4	GA	0.3869	0.5311	0.0171
S2/ST+4	CA	0.1999	0.0943	0.0409
S2/ST+4	GA	0.2839	0.4767	0.0017
Q-1/ST+4	CA	0.3894	0.5547	0.0063
Q-1/ST+4	TA	0.0933	0.0172	0.0340
KL+2/ST+4	CA	0.3767	0.5480	0.0068
L-1/ST+5	AC	0.1283	0.0290	0.0128
L-1/ST+5	AT	0.0000	0.0322	0.0019
ST+4/ST+5	AT	0.3673	0.4887	0.0496
ST+4/ST+5	CT	0.0745	0.0000	0.0055
S1/ST+5	AT	0.1060	0.0400	0.0458

S2/ST+5	CT	0.1158	0.0217	0.0158
S2/ST+5	GT	0.3280	0.4691	0.0184
Q-1/ST+5	CT	0.3321	0.4905	0.0058
Q-1/ST+5	TT	0.1116	0.0000	0.0023
KL+2/ST+5	AT	0.1371	0.0155	0.0076
KL+2/ST+5	CT	0.3069	0.4766	0.0081
S1/ST+6	AC	0.1061	0.0400	0.0446
S1/ST+6	GC	0.8939	0.9600	0.0442
S2/ST+6	CC	0.2714	0.1300	0.0053
S2/ST+6	GC	0.7286	0.8700	0.0053
D-1/ST+7	CA	0.1215	0.0130	0.0096
M+1/ST+7	TA	0.0000	0.0123	0.0298
M+1/ST+7	GG	0.6647	0.8095	0.0084
M+1/ST+7	TG	0.1309	0.0477	0.0359
L-1/ST+7	AA	0.0000	0.0121	0.0146
L-1/ST+7	AG	0.1285	0.0491	0.0472
L-1/ST+7	GG	0.6671	0.8081	0.0111
ST+4/ST+7	AG	0.3873	0.5482	0.0118
ST+5/ST+7	TA	0.1173	0.0136	0.0053
ST+5/ST+7	TG	0.3264	0.4729	0.0124
S+1/ST+7	TA	0.1356	0.0263	0.0089
S+1/ST+7	TG	0.3319	0.4910	0.0097
S2/ST+7	GG	0.6567	0.7845	0.0250
L-1/S+1	AA	0.1284	0.0318	0.0132
L-1/S+1	AT	0.0000	0.0294	0.0056
S1/S+1	AA	0.0000	0.0400	<b>0.0001</b>
S1/S+1	AT	0.1061	0.0000	0.0024
S1/S+1	GT	0.3609	0.5135	0.0132
S2/S+1	GT	0.3307	0.4623	0.0359
KL+2/S+1	AT	0.1417	0.0142	0.0027
KL+2/S+1	CT	0.3269	0.5104	0.0057
A-1/S1	TG	0.0000	0.0300	0.0170
D-1/S1	CA	0.1069	0.0000	0.0020
D-1/S1	GA	0.0000	0.0400	0.0020
D1/S1	TA	0.1061	0.0400	0.0460
I1/S1	GA	0.1059	0.0331	0.0403
I1/S1	GG	0.7308	0.8769	0.0045
M+1/S1	GA	0.1061	0.0318	0.0379
M+1/S1	GG	0.7632	0.9082	0.0023
M+1/S1	TG	0.1307	0.0518	0.0443
L-1/S1	AA	0.0000	0.0081	0.0350
L-1/S1	GA	0.1061	0.0319	0.0339
L-1/S1	GG	0.7658	0.9070	0.0036
A-1/S2	AC	0.2661	0.1300	0.0039
A-1/S2	AG	0.7227	0.8400	0.0181

D-1/S2	CC	0.1196	0.0141	0.0087
D-2/S2	CC	0.2700	0.1300	0.0043
D-2/S2	CG	0.7228	0.8598	0.0052
D1/S2	TC	0.2714	0.1300	0.0059
D1/S2	TG	0.7286	0.8600	0.0079
F+1/S2	AC	0.2575	0.1300	0.0087
F+1/S2	GG	0.6159	0.7407	0.0340
F1/S2	AC	0.2500	0.1100	0.0034
F1/S2	AG	0.7286	0.8700	0.0058
G-1/S2	TC	0.2605	0.1235	0.0066
G-1/S2	TG	0.6414	0.7749	0.0158
I1/S2	GC	0.1127	0.0400	0.0386
I1/S2	GG	0.7245	0.8700	0.0021
M+1/S2	GG	0.7286	0.8700	0.0054
L-1/S2	GG	0.7286	0.8592	0.0071
L-2/S2	GC	0.2714	0.1230	0.0021
L-2/S2	GG	0.6550	0.7870	0.0184
L1/S2	CC	0.2714	0.1300	0.0061
L1/S2	CG	0.7214	0.8600	0.0065
S1/S2	GG	0.7286	0.8700	0.0042
Q-1/S2	CG	0.7286	0.8700	0.0039
KL+1/S2	GC	0.2429	0.1100	0.0059
KL+1/S2	GG	0.7286	0.8700	0.0057
KL+2/S2	AC	0.1220	0.0233	0.0186
KL+2/S2	CG	0.5661	0.6833	0.0465
S1/T+1	AC	0.1068	0.0324	0.0342
S1/T+1	GC	0.7600	0.8934	0.0057
S2/T+1	GC	0.7233	0.8584	0.0057
Q-1/T+1	CC	0.7277	0.8602	0.0081
S1/T+2	AG	0.0000	0.0165	0.0100
S1/T+2	AT	0.1061	0.0235	0.0161
S2/T+2	CG	0.0000	0.0235	0.0237
S2/T+2	CT	0.2714	0.1065	<b>0.0010</b>
S2/T+2	GT	0.6036	0.7535	0.0068
Q-1/T+2	TG	0.0000	0.0357	<b>0.0003</b>
Q-1/T+2	TT	0.1393	0.0343	0.0088
S1/T1	AT	0.1061	0.0322	0.0354
S1/T1	GT	0.7617	0.8978	0.0057
S2/T1	GT	0.7244	0.8593	0.0097
Q-1/T1	TC	0.0000	0.0051	0.0469
Q-1/T1	CT	0.7286	0.8651	0.0057
KL+2/T1	CT	0.5834	0.7200	0.0150
S1/T2	AC	0.1059	0.0315	0.0329
S1/T2	GC	0.7895	0.9167	0.0082
S2/T2	CC	0.1674	0.0800	0.0334



S2/T2	GC	0.7243	0.8700	0.0027
Q-1/T2	CC	0.7559	0.8848	0.0068
Q-1/T2	TT	0.0000	0.0068	0.0258
D-1/V-1	CA	0.1227	0.0000	0.0015
D-1/V-1	GA	0.0131	0.0600	0.0290
D-1/V-1	CC	0.4893	0.6162	0.0445
I1/V-1	GA	0.1152	0.0323	0.0229
I1/V-1	GC	0.7217	0.8777	0.0043
M+1/V-1	GA	0.1357	0.0532	0.0308
M+1/V-1	GC	0.7336	0.8868	0.0017
L-1/V-1	AA	0.0000	0.0067	0.0147
L-1/V-1	GA	0.1357	0.0533	0.0291
L-1/V-1	GC	0.7361	0.8856	0.0018
ST+4/V-1	AA	0.0951	0.0211	0.0449
ST+4/V-1	AC	0.3881	0.5506	0.0076
ST+5/V-1	CA	0.0231	0.0600	0.0463
ST+5/V-1	TA	0.1126	0.0000	0.0017
ST+5/V-1	TC	0.3312	0.4904	0.0069
ST+6/V-1	CA	0.1357	0.0600	0.0497
ST+6/V-1	CC	0.8643	0.9400	0.0497
S2/V-1	CA	0.1357	0.0600	0.0467
S2/V-1	GC	0.7286	0.8700	0.0035
T+1/V-1	CA	0.1357	0.0543	0.0314
T+1/V-1	CC	0.7313	0.8713	0.0058
T+2/V-1	GA	0.0000	0.0251	0.0011
T+2/V-1	TA	0.1357	0.0349	0.0068
T1/V-1	CA	0.0000	0.0061	0.0492
T1/V-1	TA	0.1357	0.0539	0.0285
T1/V-1	TC	0.7321	0.8761	0.0039
T2/V-1	CA	0.1357	0.0526	0.0311
T2/V-1	TA	0.0000	0.0074	0.0275
T2/V-1	CC	0.7595	0.8955	0.0063
ST+4/V-2	CC	0.1352	0.0203	0.0015
ST+7/V-2	AC	0.1518	0.0371	0.0080
S2/V-2	CC	0.2602	0.1116	0.0027
S2/V-2	GC	0.3611	0.4784	0.0472
KL+2/V-2	AC	0.1372	0.0251	0.0047
ST+4/V-3	CG	0.1352	0.0203	0.0014
ST+7/V-3	AG	0.1448	0.0374	0.0115
S2/V-3	CG	0.2656	0.1090	0.0019
S2/V-3	GG	0.3552	0.4749	0.0452
KL+2/V-3	AG	0.1334	0.0254	0.0081
S2/V-4	CC	0.2635	0.1300	0.0095
S2/V-4	GC	0.4852	0.6039	0.0488
ST+4/V7	AC	0.2894	0.4587	0.0043

S2/V7	CG	0.2557	0.1186	0.0049
V-2/V7	CG	0.2615	0.1221	0.0101
V-3/V7	GG	0.2625	0.1152	0.0087
S2/V6	CC	0.2630	0.1230	0.0042
S2/V6	GC	0.6543	0.7870	0.0174
S2/V5	CA	0.2429	0.1100	0.0063
S2/V5	GA	0.7286	0.8700	0.0050
S2/V4	GC	0.6128	0.7546	0.0106
S2/V2	CC	0.2461	0.1100	0.0031
S2/V2	GC	0.7286	0.8700	0.0045
S2/V1	CA	0.2494	0.1100	0.0044
S2/V1	GA	0.7286	0.8700	0.0062
D-1/Q-1	CC	0.4861	0.6165	0.0427
D-1/Q-1	CT	0.1258	0.0000	0.0011
D-1/Q-1	GT	0.0135	0.0700	0.0218
I1/Q-1	AC	0.1391	0.0519	0.0430
I1/Q-1	GC	0.7216	0.8781	0.0043
I1/Q-1	GT	0.1153	0.0319	0.0223
M+1/Q-1	GC	0.7300	0.8761	0.0023
M+1/Q-1	TT	0.0000	0.0061	0.0455
L-1/Q-1	AC	0.1282	0.0552	0.0496
L-1/Q-1	GC	0.7325	0.8748	0.0025
L-1/Q-1	AT	0.0000	0.0060	0.0162
L-1/Q-1	GT	0.1393	0.0640	0.0491

**TABLE 26(CON'T)**

BHR				
US Population				
SNP COMBINATION	HAPLOTYPE	FREQUENCIES		P-VALUE
		CNTL	CASE	
A-1/M+1	AT	0.0773	0.2500	0.0082
D-1/M+1	GT	0.0705	0.2500	0.0079
D-2/M+1	CG	0.9138	0.7500	0.0179
D-2/M+1	CT	0.0795	0.2500	0.0133
D1/M+1	TG	0.9200	0.7500	0.0144
D1/M+1	TT	0.0800	0.2500	0.0144
L-1/M+1	GG	0.9200	0.7500	0.0129
L-1/M+1	AT	0.0800	0.2500	0.0124
KL+2/M+1	CG	0.6284	0.3571	0.0045
KL+2/M+1	CT	0.0794	0.2500	0.0041
A-1/L-1	AA	0.0773	0.2500	0.0111
D-1/L-1	GA	0.0705	0.2500	0.0065
D-2/L-1	CA	0.0795	0.2500	0.0113
D-2/L-1	CG	0.9138	0.7500	0.0163

D1/L-1	TA	0.0800	0.2500	0.0154
D1/L-1	TG	0.9200	0.7500	0.0154
KL+2/L-1	CA	0.0794	0.2500	0.0030
KL+2/L-1	CG	0.6284	0.3571	0.0047
L-1/L1	AC	0.0800	0.2500	0.0115
L-1/L1	GC	0.9135	0.7500	0.0122
M+1/ST+7	GG	0.6794	0.4643	0.0205
M+1/ST+7	TG	0.0786	0.2500	0.0054
L-1/ST+7	AG	0.0786	0.2500	0.0051
L-1/ST+7	GG	0.6794	0.4643	0.0200
S2/S+1	CA	0.0376	0.2754	0.0062
A-1/S2	AC	0.2405	0.4643	0.0250
D1/S2	TC	0.2468	0.4643	0.0276
D1/S2	TG	0.7532	0.5357	0.0276
F1/S2	AC	0.1948	0.4286	0.0111
F1/S2	AG	0.7532	0.5357	0.0246
Q-1/S2	CC	0.0779	0.2500	0.0107
Q-1/S2	CG	0.7532	0.5357	0.0203
T1/T+1	TC	0.9078	0.7143	0.0116
T1/T+1	CT	0.0779	0.2857	0.0039
KL+2/T+1	CC	0.6356	0.3643	0.0041
KL+2/T+1	CT	0.0722	0.2429	0.0106
T1/T+2	CT	0.0779	0.2857	0.0029
A-1/T1	AC	0.0751	0.2857	0.0037
A-1/T1	AT	0.8795	0.7143	0.0360
D-1/T1	GC	0.0678	0.2398	0.0069
D-2/T1	CC	0.0779	0.2857	0.0066
D-2/T1	CT	0.9154	0.7143	0.0084
D1/T1	TC	0.0779	0.2857	0.0058
D1/T1	TT	0.9221	0.7143	0.0058
F+1/T1	AC	0.0677	0.2420	0.0077
F+1/T1	GT	0.6648	0.4206	0.0251
F1/T1	AC	0.0779	0.2857	0.0059
F1/T1	AT	0.8701	0.6786	0.0151
G-1/T1	TC	0.0699	0.2857	0.0020
G-1/T1	TT	0.8479	0.6429	0.0120
I1/T1	AC	0.0710	0.2489	0.0090
I1/T1	GT	0.8674	0.6774	0.0166
M+1/T1	TC	0.0779	0.2500	0.0126
M+1/T1	GT	0.9221	0.7143	0.0059
L-1/T1	AC	0.0779	0.2500	0.0099
L-1/T1	GT	0.9221	0.7143	0.0040
L-2/T1	GC	0.0774	0.2857	0.0023
L-2/T1	GT	0.8558	0.6429	0.0067
L1/T1	CC	0.0779	0.2857	0.0061

L1/T1	CT	0.9156	0.7143	0.0080
ST+4/T1	AC	0.0779	0.2857	0.0039
ST+5/T1	CC	0.0779	0.2242	0.0125
ST+6/T1	CC	0.0779	0.2857	0.0052
ST+6/T1	CT	0.9091	0.7143	0.0106
ST+7/T1	GC	0.0779	0.2857	0.0031
ST+7/T1	GT	0.6801	0.4286	0.0139
S+1/T1	AC	0.0779	0.2235	0.0133
S1/T1	GC	0.0779	0.2857	0.0036
S1/T1	GT	0.8182	0.5556	0.0032
S2/T1	CC	0.0779	0.2451	0.0116
S2/T1	GT	0.7532	0.4951	0.0070
Q-1/T1	CC	0.0779	0.2857	0.0041
Q-1/T1	CT	0.7532	0.5000	0.0075
KL+1/T1	GC	0.0779	0.2857	0.0055
KL+1/T1	GT	0.8636	0.6786	0.0213
KL+2/T1	CC	0.0779	0.2857	0.0039
KL+2/T1	CT	0.6299	0.3214	0.0022
M+1/T2	GC	0.9221	0.7500	0.0051
M+1/T2	TT	0.0779	0.2143	0.0277
L-1/T2	GC	0.9221	0.7500	0.0055
L-1/T2	AT	0.0779	0.2143	0.0330
T1/T2	CC	0.0000	0.0714	0.0213
T1/T2	TC	0.9221	0.7143	0.0025
T1/T2	CT	0.0779	0.2143	0.0310
KL+2/T2	CC	0.6343	0.3929	0.0091
KL+2/T2	CT	0.0735	0.2143	0.0135
S2/V-1	CC	0.0779	0.2500	0.0109
S2/V-1	GC	0.7532	0.5357	0.0171
T1/V-1	CC	0.0779	0.2857	0.0055
T1/V-1	TC	0.7508	0.5000	0.0126
T1/V-2	CC	0.0779	0.2857	0.0024
T1/V-3	CG	0.0779	0.2857	0.0036
M+1/V-4	GC	0.6902	0.4643	0.0160
M+1/V-4	TC	0.0793	0.2500	0.0032
L-1/V-4	AC	0.0793	0.2500	0.0045
L-1/V-4	GC	0.6902	0.4643	0.0148
S2/V-4	CC	0.2468	0.4643	0.0194
S2/V-4	GC	0.5240	0.2500	0.0039
T1/V-4	CC	0.0779	0.2857	0.0036
T1/V-4	TC	0.6916	0.4286	0.0080
A-1/V7	AG	0.3226	0.5357	0.0459
D1/V7	TC	0.6776	0.4643	0.0392
D1/V7	TG	0.3224	0.5357	0.0392
F+1/V7	AG	0.3020	0.5357	0.0102

ST+6/V7	CC	0.6777	0.4643	0.0374
ST+6/V7	CG	0.3093	0.5357	0.0337
T1/V7	TC	0.6784	0.4206	0.0164
T1/V7	CG	0.0779	0.2420	0.0120
V-4/V7	CC	0.4984	0.2192	0.0032
V-4/V7	CG	0.2716	0.4951	0.0214
V5/V7	AG	0.2839	0.5357	0.0146
T1/V6	CC	0.0779	0.2500	0.0092
T1/V6	TC	0.8279	0.6429	0.0326
F+1/V5	AA	0.2817	0.5357	0.0319
I1/V5	AA	0.0897	0.2857	0.0064
M+1/V5	TA	0.0801	0.2500	0.0117
L-1/V5	AA	0.0801	0.2500	0.0107
S2/V5	CA	0.2021	0.4643	0.0046
S2/V5	GA	0.7446	0.5357	0.0378
T+1/V5	TA	0.0790	0.2308	0.0212
T1/V5	CA	0.0779	0.2857	0.0058
T1/V5	TA	0.8686	0.7143	0.0344
T2/V5	TA	0.0745	0.2143	0.0260
F+1/V4	AG	0.1017	0.2500	0.0463
M+1/V4	GC	0.7136	0.5000	0.0164
M+1/V4	TC	0.0786	0.2500	0.0061
T1/V4	CC	0.0779	0.2857	0.0041
T1/V4	TC	0.7143	0.4643	0.0125
T1/V3	CT	0.0779	0.2857	0.0056
T1/V3	TT	0.6883	0.4643	0.0159
S2/V2	CC	0.1883	0.4286	0.0082
S2/V2	GC	0.7532	0.5357	0.0259
T1/V2	CC	0.0779	0.2857	0.0048
T1/V2	TC	0.8636	0.6786	0.0219
S2/V1	CA	0.1851	0.4286	0.0088
S2/V1	GA	0.7532	0.5357	0.0245
T1/V1	CA	0.0779	0.2857	0.0066
T1/V1	TA	0.8611	0.6786	0.0242
I1/KL+2	AC	0.1269	0.2857	0.0377
I1/KL+2	GC	0.5809	0.3214	0.0058

**TABLE 27**

Haplotypes for 15-SNP Combination D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7	Freq_Control	Freq_Case BHR	Pval-2sided
Combined US & UK			
CAGCGGTCACTCACC	0.0000	0.0078	0.22
TAACACTCACTGACG	0.0016	0.0000	0.84
TAACGCCCACTCACG	0.0075	0.0156	0.62

TAACGCCCACTGACC	0.0023	0.0000	0.86
TAACGCCTACTCACG	0.0830	0.0859	0.89
TAACGCCTACTCATG	0.0049	0.0000	0.46
TAACGCCTACTGACG	0.0082	0.0000	0.24
TAACGCTCACCCACC	0.0023	0.0000	1.00
TAACGCTCACCGACC	0.0000	0.0078	0.14
TAACGCTCTTCGGCG	0.0046	0.0000	0.75
TAACGGTCACTCACC	0.0032	0.0000	0.32
TAGCACTCACTCACC	0.0023	0.0000	0.73
TAGCACTCACTCACG	0.0026	0.0000	0.29
TAGCACTCACTGACG	0.0971	0.0703	0.37
TAGCGCCTACTCACG	0.0025	0.0000	0.32
TAGCGCCTACTCATG	0.0022	0.0000	0.82
TAGCGCTCACTCACG	0.0029	0.0000	0.27
TAGCGCTCACTCATG	0.0002	0.0000	0.92
TAGCGCTCACTGACC	0.0029	0.0000	0.67
TAGCGCTCACTGACG	0.0009	0.0000	0.77
TAGCGCTCACTGATG	0.0000	0.0000	0.41
TAGCGCTCTTCGGCG	0.0023	0.0000	1.00
TAGCGGCCACTCACG	0.0000	0.0078	0.22
TAGCGGCCACTCATC	0.0000	0.0078	0.22
TAGCGGCTACTGATG	0.0023	0.0000	1.00
TAGCGGTCACCCACC	0.1762	0.1677	0.83
TAGCGGTCACCCACG	0.0000	0.0000	0.15
TAGCGGTCACCGACG	0.0065	0.0078	0.91
TAGCGGTCACTCACC	0.3648	0.4023	0.45
TAGCGGTCACTCACG	0.0024	0.0159	0.09
TAGCGGTCACTCATG	0.0707	0.0859	0.59
TAGCGGTCACTCGCC	0.0023	0.0000	0.50
TAGCGGTCACTGACC	0.0993	0.0859	0.70
TAGCGGTCACTGACG	0.0027	0.0000	0.87
TAGTGGTCACCCACC	0.0000	0.0078	0.08
TAGTGGTCACTCACC	0.0063	0.0000	0.70
TAGTGGTCACTGACC	0.0006	0.0000	0.48
TGACGCTCTTCCACG	0.0032	0.0000	0.29
TGACGCTCTTCCGCC	0.0026	0.0000	0.68
TGACGCTCTTCCGCG	0.0169	0.0000	0.28
TGACGCTCTTCCGTG	0.0059	0.0000	0.49
TGACGCTCTTCGACG	0.0014	0.0000	0.89
TGACGCTCTTCGGCG	0.0023	0.0234	0.02
Overall Test			0.61

**TABLE 27(CON'T)**

Haplotypes for 15-SNP Combination D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7	Freq_Control	Freq_Case BHR	Pval-2sided
UK			
CAGCGGTCACTCACC	0.0000	0.0100	0.28
TAACACTCACTGACG	0.0022	0.0000	0.99
TAACGCCCCACTCACC	0.0115	0.0100	0.82
TAACGCCCCACTGACC	0.0036	0.0000	1.00
TAACGCCTACTCACC	0.0895	0.0500	0.29
TAACGCCTACTCATG	0.0071	0.0000	0.77
TAACGCCTACTGACG	0.0132	0.0000	0.30
TAACGCTCACCACC	0.0036	0.0000	0.99
TAACGCTCACCACC	0.0000	0.0100	0.15
TAACGCTCTTCGGCG	0.0071	0.0000	0.78
TAACGGTCACTCACC	0.0050	0.0000	0.28
TAGCACTCACTCACC	0.0041	0.0000	0.41
TAGCACTCACTGACG	0.0972	0.0400	0.08
TAGCGCCTACTCATG	0.0036	0.0000	0.26
TAGCGCTCACTGACC	0.0044	0.0000	0.64
TAGCGCTCACTGACG	0.0028	0.0000	0.63
TAGCGCTCACTGATG	0.0000	0.0000	0.41
TAGCGGCCACTCACC	0.0000	0.0100	0.25
TAGCGGCTACTGATG	0.0036	0.0000	1.00
TAGCGGTCACCCACC	0.1808	0.1472	0.49
TAGCGGTCACCGACC	0.0000	0.0055	0.15
TAGCGGTCACCGACG	0.0062	0.0098	0.90
TAGCGGTCACTCACC	0.3569	0.4722	0.08
TAGCGGTCACTCACC	0.0000	0.0207	0.03
TAGCGGTCACTCATG	0.0687	0.0900	0.54
TAGCGGTCACTGACC	0.0958	0.0947	0.97
TAGCGGTCACTGACG	0.0045	0.0000	0.79
TAGTGGTCACCCACC	0.0000	0.0100	0.15
TAGTGGTCACTCACC	0.0049	0.0000	0.88
TAGTGGTCACTGACC	0.0023	0.0000	0.52
TGACGCTCTTCGGCC	0.0036	0.0000	1.00
TGACGCTCTTCGGCG	0.0143	0.0000	0.42
TGACGCTCTTCGGCG	0.0036	0.0200	0.12
Overall Test			0.27

**TABLE 27(CON'T)**

Haplotypes for 15-SNP Combination D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7	Freq_Control	Freq_Case BHR	Pval-2sided
US			
TAACGCCCCACTCACC	0.0000	0.0357	0.038
TAACGCCTACTCACC	0.0714	0.2143	0.030

TAACGGTCACCGACG	0.0000	0.0000	0.920
TAACGGTCTCCGACG	0.0000	0.0000	0.920
TAGCACTCACTCACC	0.0065	0.0000	0.169
TAGCACTCACTGACG	0.0974	0.1786	0.275
TAGCGCTCACTCACG	0.0065	0.0000	0.992
TAGCGCTCACTCACG	0.0054	0.0000	0.547
TAGCGCTCACTCATG	0.0005	0.0000	0.781
TAGCGCTCACTCGCG	0.0003	0.0000	0.280
TAGCGCTCACTCGTG	0.0002	0.0000	0.296
TAGCGCTCTTCCGCG	0.0065	0.0000	0.984
TAGCGGCCACTCATC	0.0000	0.0357	0.134
TAGCGGTCACCCACC	0.1688	0.2143	0.543
TAGCGGTCACCGACG	0.0064	0.0000	0.118
TAGCGGTCACTCACC	0.3858	0.2143	0.071
TAGCGGTCACTCACG	0.0066	0.0000	0.721
TAGCGGTCACTCATG	0.0725	0.0357	0.655
TAGCGGTCACTCGCC	0.0068	0.0000	0.460
TAGCGGTCACTGACC	0.0997	0.0000	0.099
TAGCGGTCACTGATG	0.0000	0.0357	<b>0.022</b>
TAGCGGTCTCCGACG	0.0000	0.0000	0.920
TAGTGGTCACTCACC	0.0065	0.0000	1.000
TGACACTCTTCGACG	0.0000	0.0089	0.093
TGACACTCTTCGGCG	0.0000	0.0089	0.093
TGACGCTCTTCACG	0.0089	0.0000	0.189
TGACGCTCTTCGCG	0.0205	0.0000	0.804
TGACGCTCTTCGTG	0.0184	0.0000	0.655
TGACGCTCTTCGACG	0.0042	0.0089	0.922
TGACGCTCTTCGGCG	0.0000	0.0089	0.093
Overall Test			0.105

#### **EXAMPLE 14: Transmission Disequilibrium Test (TDT)**

- To ensure that the significant association observed in the case-control studies was not an artifact due to population admixture, a transmission disequilibrium test (TDT) was conducted. By selecting a single affected offspring in each family, the TDT performed as a family based test of association (due to linkage disequilibrium) in the presence of linkage. The TDT determined whether a particular allele was preferentially transmitted to an affected individual, as compared to what would be expected by chance. Only heterozygous parents were considered informative for the TDT. In addition, heterozygous parents transmitting different alleles to two affected offspring



were ignored. Accordingly, the TDT was based on the same families that contributed to the linkage signal. The significance levels were estimated by Markov Chain Monte Carlo simulation methods as implemented in TDTEX from the S.A.G.E. program (Department of Epidemiology and Biostatistics, Rammelkamp Center for Education and Research, MetroHealth Campus, Case Western Reserve University, Cleveland, OH (1997)).

1. Asthma Phenotype: Eleven candidate SNPs were typed in the extended population in order to confirm the association seen in the case/control study. The eleven SNPs were in Gene 216 exons L-1, S1, S2, ST+4, ST+7, T1, V-4, V-3, V-1, V1 and V4. In addition to analyzing SNPs separately, SNP haplotypes (all 2-at-a-time, all 3-at-a-time and selected 4-at-a-time and 5-at-a-time) were constructed based on family data with the program GENEHUNTER (Kruglyak et al., 1996). This served to increase the informativeness of the single SNPs, as only heterozygote parents contributed information to the TDT. These haplotypes were used as "alleles" in subsequent TDT analyses. In addition, p-values obtained from the TDT analyses were compared to the p-values obtained from the haplotyping in the case/control setting. To check for consistency, the p-values were recorded to compare the haplotype frequencies between the cases and controls of the over-transmitted alleles/haplotypes.

The TDT results strongly supported the association previously observed in the case control studies (Table 28). Five of the eleven SNPs showed alleles that were preferentially transmitted to affected offspring ( $p < 0.05$  to  $p < 0.005$ ) in either the combined or one of the separate populations. When these SNPs were haplotyped together, most combinations had a haplotype that was preferentially transmitted to affected offspring in either the combined or one of the separate populations ( $p < 0.05$  to  $p = 0.0002$ ). The most significant SNP in the combined population was S2 ( $p = 0.0049$ ) while the most significant 2-at-a-time haplotype included SNPs S2/V-1 ( $p = 0.0011$ ). The most significant haplotype in the combined population included SNPs S2/ST+7/V-1 ( $p = 0.0006$ ). In the UK population, the most significant SNP was S1 ( $p = 0.0043$ ),

while the most significant 2-at-a-time haplotype included SNPs ST+7/T1 ( $p = 0.0013$ ). The most significant haplotype in the UK population included SNPs S2/ST+7/T1 ( $p = 0.0002$ ). In the US population, the most significant SNP was S2 ( $p = 0.0351$ ) and the most significant haplotype included SNPs S2/V-1 ( $p = 0.0106$ ). The lower significance in the US was most likely due to the smaller sample size in that population and to the reduced power of the TDT versus the case-control study design.

Importantly, for almost all of the significant single SNP or multiple SNP haplotypes, the allele that was over-transmitted in either the combined population or in the UK sample was more frequent in the cases than in the controls. A summary of the TDT analyses and a comparison between the case/control and TDT results are presented in Table 28.

2. Bronchial Hyper-responsiveness: The TDT analyses were repeated using only those asthmatic pairs that satisfied the additional criteria of having a  $PC_{20} \leq 16$  mg/ml (Table 29). The vast majority of single SNP and multiple SNP haplotypes showed increased significance with the more restricted phenotype. The most significant SNP in the combined population was S2 ( $p = 0.0029$ ). The most significant 2-at-a-time haplotypes included SNPs S1/T1 as well as SNPs T1/V4 ( $p = 0.0005$ ), while the most significant 3-at-a-time haplotype included SNPs ST+7/T1/V4 ( $p = 0.0003$ ). The most significant haplotypes included SNPs S2/ST+7/T1/V-3/V-1 as well as SNPs S2/ST+7/T1/V-1/V4 ( $p = 0.00013$ ). In the UK population, the most significant SNP was S2 ( $p = 0.0055$ ). The most significant 2-at-a-time haplotype included SNPs S2/ST+7 ( $p = 0.00013$ ), while the most significant 3-at-a-time haplotype included SNPs ST+7/T1/V4 ( $p = 0.000019$ ). Increased significance was observed in both the selected 4 and 5-at-a-time haplotypes. The most significant 4-at-a-time haplotype included SNPs S2/ST+7/T1/V-1 ( $p = 0.000009$ ), while the most significant 5-at-a-time haplotype included SNPs S2/ST+7/T1/V-3/V-1 ( $p = 0.000001$ ). In the US population, the most significant SNP was L-1 ( $p = 0.0386$ ) and the most significant haplotype included SNPs L-1/ST+7 ( $p = 0.0423$ ). Similar to the yes/no phenotype, the over-transmitted

alleles in the TDT were more frequent in the cases for the majority of the alleles in both the combined and UK population. In summary, the analysis of single SNPs and SNP haplotypes by the TDT test provided confirmatory evidence for Gene 216 as an asthma susceptibility gene.

- 5 It is noted that for Tables 28 and 29, the haplotypes are written without slashes separating each allele. Thus, the haplotype that is G/T/G/C/C is written as GTGCC in Table 28. This represents the short-hand designations for the haplotypes and is not, in any way, meant to represent contiguous nucleotide sequences.

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**TABLE 28**

Asthma Yes/No Combined							
SNP(s)	Over-Transmitted Allele or Haplo	T	NT	TDT p-value	Case/Cntl p-value	Case freq	Cntl freq
L-1	G	37	31	0.5446	1.0000	89%	89%
S1	G	37	20	0.0331	0.0233	95%	89%
S2	G	73	42	<b>0.0049</b>	0.0662	80%	74%
ST+4	A	93	93	1.0000	0.0313	60%	51%
ST+7	G	59	41	0.0886	0.0160	86%	78%
T1	T	43	27	0.0722	0.9025	88%	89%
V-4	G	69	68	1.0000	0.4713	27%	24%
V-3	A	83	76	0.6343	0.6834	39%	37%
V-1	C	43	27	0.0722	0.0055	92%	85%
V1	A	7	7	1.0000	0.2515	98%	96%
V4	C	73	55	0.1326	0.0336	84%	77%
L-1/S1	GG	64	38	0.0167	0.0925	84%	78%
L-1/S2	GG	78	46	0.0083	0.0787	80%	74%
L-1/ST+4	GA	96	89	0.5802	0.1040	49%	42%
L-1/ST+7	GG	85	58	0.0517	0.0426	75%	67%
L-1/T1	GT	40	27	0.0841	0.6682	88%	89%
L-1/V-4	GC	98	81	0.3053	0.4698	62%	65%
L-1/V-3	GG	94	87	0.6144	0.6823	50%	52%
L-1/V-1	GC	71	42	0.0094	0.0306	81%	74%
L-1/V1	GA	43	30	0.2394	0.5631	87%	85%
L-1/V4	GC	84	58	0.0615	0.0937	72%	66%
S1/S2	GG	74	40	0.0020	0.0649	80%	74%
S1/ST+4	GA	99	88	0.1935	0.0012	55%	42%
S1/ST+7	GG	59	40	0.0823	0.0213	85%	78%
S1/T1	GT	72	38	0.0016	0.1232	83%	78%
S1/V-4	GC	88	68	0.0671	0.4747	68%	65%
S1/V-3	GG	93	81	0.1306	0.4049	56%	53%

S1/V-3	GA	83	77	0.1306	0.6842	39%	37%
S1/V-1	GC	44	26	0.0540	0.0042	92%	85%
S1/V1	GA	43	26	0.0565	0.0088	93%	86%
S1/V4	GC	75	57	0.1318	0.0302	83%	76%
S2/ST+4	GA	112	77	0.0165	0.0019	43%	31%
S2/ST+7	GG	95	56	0.0041	0.0746	73%	67%
S2/T1	GT	78	42	0.0029	0.0844	79%	73%
S2/V-4	GC	114	73	0.0017	0.4269	53%	50%
S2/V-3	GG	105	70	0.0034	0.1681	43%	37%
S2/V-1	GC	77	40	0.0011	0.0690	80%	74%
S2/V1	GA	74	40	0.0019	0.0638	80%	74%
S2/V4	GC	90	54	0.0039	0.0174	71%	62%
ST+4/ST+7	AG	104	86	0.2999	0.0006	55%	40%
ST+4/T1	AT	101	82	0.1920	0.1333	48%	42%
ST+4/V-4	AC	92	89	0.9431	0.0489	60%	52%
ST+4/V-3	AG	95	85	0.3543	0.0559	59%	52%
ST+4/V-1	AC	103	88	0.2800	0.0006	55%	41%
ST+4/V1	CA	90	88	0.9281	0.0972	38%	45%
ST+4/V4	AC	102	88	0.2943	0.0010	55%	41%
ST+7/T1	GT	86	52	0.0060	0.0537	74%	67%
ST+7/V-4	GC	99	76	0.0819	0.1027	65%	59%
ST+7/V-3	GG	103	81	0.1801	0.0507	54%	47%
ST+7/V-1	GC	63	44	0.0889	0.0188	85%	78%
ST+7/V1	GA	59	43	0.2206	0.0153	86%	78%
ST+7/V4	GC	83	62	0.1327	0.0046	76%	66%
T1/V-4	TC	95	74	0.1090	0.4155	61%	64%
T1/V-3	TG	97	80	0.2083	0.6220	50%	52%
T1/V-1	TC	80	46	0.0053	0.0467	81%	74%
T1/V1	TA	49	31	0.0738	0.6598	86%	85%
T1/V4	TC	97	60	0.0064	0.1334	72%	66%
V-4/V-3	CA	52	43	0.2513	0.6973	12%	13%
V-4/V-1	GG	6	1	0.2513	0.3277	0%	0%
V-4/V1	CC	91	70	0.0560	0.2280	65%	61%
V-4/V4	CA	70	66	0.8701	0.8035	71%	72%
V-4/V4	CC	97	78	0.3465	0.3691	57%	53%
V-3/V-1	GC	98	83	0.1240	0.1818	54%	48%
V-3/V1	GA	83	80	0.8925	0.9739	59%	59%
V-3/V4	GC	98	79	0.1049	0.4273	54%	51%
V-1/V1	CA	43	29	0.1385	0.0058	92%	85%
V-1/V4	CC	76	57	0.1440	0.0009	83%	73%
V1/V4	AC	77	55	0.0972	0.0024	84%	74%
L-1/S1/S2	GGG	70	41	0.0124	0.0810	80%	74%
L-1/S1/ST+4	GGA	90	70	0.1572	0.0032	43%	32%
L-1/S1/ST+7	GGG	76	51	0.0826	0.0368	75%	67%
L-1/S1/T1	GGT	63	37	0.0170	0.1622	83%	78%
L-1/S1/V-4	GGC	99	68	0.0393	0.5521	57%	54%
L-1/S1/V-3	GGG	89	72	0.1596	0.4148	45%	42%
L-1/S1/V-1	GGC	69	40	0.0166	0.0268	82%	74%
L-1/S1/V1	GGA	67	40	0.0260	0.0303	82%	75%

L-1/S1/V4	GGC	83	58	0.0956	0.0831	72%	66%
L-1/S2/ST+4	GGA	96	67	0.0428	0.0016	43%	31%
L-1/S2/ST+7	GGG	89	55	0.0072	0.0949	73%	67%
L-1/S2/T1	GGT	71	39	0.0055	0.1188	79%	74%
L-1/S2/V-4	GGC	105	68	0.0088	0.4614	53%	50%
L-1/S2/V-3	GGG	93	66	0.0257	0.1716	42%	37%
L-1/S2/V-1	GGC	73	41	0.0056	0.0866	80%	74%
L-1/S2/V1	GGA	72	41	0.0097	0.0765	80%	74%
L-1/S2/V4	GGC	81	53	0.0323	0.0135	71%	62%
L-1/ST+4/ST+7	GAG	97	72	0.2083	0.0013	44%	31%
L-1/ST+4/T1	GAT	87	75	0.2354	0.1679	48%	42%
L-1/ST+4/V-4	GAC	95	81	0.6248	0.1018	49%	42%
L-1/ST+4/V-3	GAG	91	78	0.5715	0.1123	48%	42%
L-1/ST+4/V-1	GAC	93	72	0.1470	0.0020	43%	31%
L-1/ST+4/V1	GAA	89	81	0.5655	0.1157	49%	42%
L-1/ST+4/V4	GAC	93	70	0.1319	0.0051	43%	32%
L-1/ST+7/T1	GGT	77	48	0.0131	0.0767	74%	67%
L-1/ST+7/V-4	GGC	107	75	0.0670	0.1309	54%	48%
L-1/ST+7/V-3	GGG	99	70	0.0847	0.0549	43%	36%
L-1/ST+7/V-1	GGC	81	53	0.0311	0.0516	74%	67%
L-1/ST+7/V1	GGA	77	52	0.0929	0.0361	75%	67%
L-1/ST+7/V4	GGC	89	61	0.0986	0.0141	65%	56%
L-1/T1/V-4	GTC	89	69	0.0344	0.3591	61%	64%
L-1/T1/V-3	GTG	84	74	0.0748	0.5549	49%	52%
L-1/T1/V-1	GTC	70	39	0.0033	0.0654	80%	74%
L-1/T1/V1	GTA	44	28	0.1126	0.7542	86%	85%
L-1/T1/V4	GTC	84	57	0.0378	0.1764	71%	66%
L-1/V-4/V-3	GCG	93	86	0.2018	0.6863	50%	52%
L-1/V-4/V-3	GCA	49	38	0.2018	0.6803	12%	13%
L-1/V-4/V-1	GCC	102	69	0.0264	0.2783	54%	50%
L-1/V-4/V1	GCA	91	73	0.3709	0.7722	60%	61%
L-1/V-4/V4	GCC	96	64	0.0834	0.5577	45%	43%
L-1/V-3/V-1	GGC	92	70	0.0389	0.1787	43%	37%
L-1/V-3/V1	GGA	86	77	0.5533	0.9622	48%	48%
L-1/V-3/V4	GGC	93	69	0.1149	0.6176	43%	41%
L-1/V-1/V1	GCA	69	42	0.0300	0.0234	82%	74%
L-1/V-1/V4	GCC	85	58	0.0632	0.0089	72%	62%
L-1/V1/V4	GAC	86	57	0.0646	0.0123	72%	63%
S1/S2/ST+4	GGA	99	69	0.0296	0.0041	43%	31%
S1/S2/ST+7	GGG	86	48	0.0037	0.0958	73%	67%
S1/S2/T1	GGT	76	42	0.0091	0.0862	79%	73%
S1/S2/V-4	GGC	104	66	0.0058	0.4350	53%	50%
S1/S2/V-3	GGG	94	65	0.0180	0.1734	43%	37%
S1/S2/V-1	GGC	75	40	0.0028	0.0669	80%	74%
S1/S2/V1	GGA	73	40	0.0032	0.0679	80%	74%
S1/S2/V4	GGC	89	54	0.0031	0.0296	70%	62%
S1/ST+4/ST+7	GAG	90	81	0.3274	0.0007	54%	41%
S1/ST+4/ST+7	GCG	76	66	0.3274	0.1272	31%	37%
S1/ST+4/T1	GAT	103	73	0.0296	0.0046	43%	32%

S1/ST+4/V-4	GAC	93	78	0.2035	0.0017	54%	42%
S1/ST+4/V-3	GAG	95	76	0.1558	0.0020	54%	42%
S1/ST+4/V-1	GAC	100	87	0.4802	0.0019	54%	41%
S1/ST+4/V1	GAA	98	88	0.3370	0.0012	55%	42%
S1/ST+4/V4	GAC	100	89	0.5596	0.0005	54%	41%
S1/ST+7/T1	GGT	84	48	0.0065	0.0555	74%	67%
S1/ST+7/V-4	GGC	88	67	0.1482	0.1176	65%	59%
S1/ST+7/V-3	GGG	90	75	0.1843	0.0676	54%	47%
S1/ST+7/V-1	GGC	61	40	0.0749	0.0178	85%	78%
S1/ST+7/V1	GGA	58	40	0.1649	0.0192	85%	78%
S1/ST+7/V4	GGC	82	62	0.2201	0.0068	76%	66%
S1/T1/V-4	GTC	107	69	0.0041	0.6112	56%	54%
S1/T1/V-3	GTG	101	72	0.0248	0.4429	44%	41%
S1/T1/V-1	GTC	77	41	0.0030	0.0351	81%	74%
S1/T1/V1	GTA	75	41	0.0041	0.0550	81%	75%
S1/T1/V4	GTC	96	60	0.0120	0.1214	72%	66%
S1/V-4/V-3	GCG	90	80	0.2072	0.3996	56%	53%
S1/V-4/V-3	GCA	47	37	0.2072	0.6561	11%	13%
S1/V-4/V-1	GCC	90	68	0.0936	0.2473	65%	61%
S1/V-4/V1	GCA	89	68	0.1044	0.2773	66%	62%
S1/V-4/V4	GCC	97	79	0.3192	0.4350	56%	53%
S1/V-3/V-1	GGC	96	80	0.1266	0.1910	54%	48%
S1/V-3/V1	GGA	94	79	0.1781	0.2146	54%	49%
S1/V-3/V4	GGC	97	80	0.2252	0.4951	54%	51%
S1/V-1/V1	GCA	42	26	0.0900	0.0047	92%	85%
S1/V-1/V4	GCC	76	57	0.1512	0.0012	83%	73%
S1/V1/V4	GAC	77	56	0.1683	0.0020	83%	73%
S2/ST+4/ST+7	GAG	100	69	0.1005	0.0033	43%	32%
S2/ST+4/T1	GAT	100	66	0.0388	0.0020	43%	31%
S2/ST+4/V-4	GAC	102	65	0.0217	0.0028	43%	31%
S2/ST+4/V-3	GAG	104	64	0.0093	0.0029	42%	31%
S2/ST+4/V-1	GAC	103	67	0.0191	0.0022	43%	31%
S2/ST+4/V1	GAA	101	69	0.0126	0.0031	43%	32%
S2/ST+4/V4	GAC	102	68	0.0387	0.0021	43%	31%
S2/ST+7/T1	GGT	90	48	0.0039	0.0984	72%	67%
S2/ST+7/V-4	GGC	109	72	0.0143	0.1733	53%	48%
S2/ST+7/V-3	GGG	100	64	0.0091	0.0624	43%	35%
S2/ST+7/V-1	GGC	91	48	0.0006	0.0763	73%	67%
S2/ST+7/V1	GGA	88	48	0.0017	0.0659	73%	67%
S2/ST+7/V4	GGC	95	54	0.0023	0.0288	64%	55%
S2/T1/V-4	GTC	104	62	0.0019	0.4882	52%	50%
S2/T1/V-3	GTG	97	62	0.0060	0.2075	42%	37%
S2/T1/V-1	GTC	79	42	0.0042	0.0814	79%	74%
S2/T1/V1	GTA	77	42	0.0035	0.0922	79%	73%
S2/T1/V4	GTC	91	54	0.0111	0.0175	71%	62%
S2/V-4/V-3	GCG	98	69	0.0093	0.1562	43%	37%
S2/V-4/V-1	GCC	107	66	0.0019	0.4078	53%	50%
S2/V-4/V1	GCA	105	66	0.0029	0.4168	53%	50%
S2/V-4/V4	GCC	99	61	0.0093	0.2022	44%	39%

S2/V-3/V-1	GGC	99	65	0.0065	0.1670	43%	37%
S2/V-3/V1	GGA	97	65	0.0065	0.1578	43%	37%
S2/V-3/V4	GGC	100	63	0.0050	0.1658	43%	37%
S2/V-1/V1	GCA	75	40	0.0027	0.0627	80%	74%
S2/V-1/V4	GCC	89	54	0.0079	0.0197	71%	62%
S2/V1/V4	GAC	89	54	0.0025	0.0185	71%	62%
ST+4/ST+7/T1	AGT	96	70	0.0457	0.0029	43%	31%
ST+4/ST+7/V-4	AGC	97	80	0.4361	0.0009	54%	40%
ST+4/ST+7/V-3	AGG	98	78	0.2168	0.0011	54%	41%
ST+4/ST+7/V-1	AGC	93	82	0.4387	0.0013	55%	41%
ST+4/ST+7/V-1	CGC	77	68	0.4387	0.1220	31%	37%
ST+4/ST+7/V1	AGA	91	81	0.5479	0.0008	55%	41%
ST+4/ST+7/V1	CGA	75	68	0.5479	0.1043	31%	38%
ST+4/ST+7/V4	AGC	94	82	0.4633	0.0013	54%	41%
ST+4/T1/V-4	ATC	93	74	0.2170	0.1338	48%	42%
ST+4/T1/V-3	ATG	96	70	0.0648	0.1383	48%	42%
ST+4/T1/V-1	ATC	108	74	0.0307	0.0039	43%	31%
ST+4/T1/V1	ATA	100	83	0.2959	0.1454	48%	42%
ST+4/T1/V4	ATC	106	73	0.0451	0.0079	42%	32%
ST+4/V-4/V-3	CCA	45	38	0.1845	0.4920	11%	13%
ST+4/V-4/V-1	ACC	96	79	0.1591	0.0010	55%	41%
ST+4/V-4/V1	CCA	45	41	0.7601	0.0019	11%	20%
ST+4/V-4/V4	ACC	95	76	0.2691	0.0017	54%	41%
ST+4/V-3/V-1	AGC	98	77	0.1923	0.0019	54%	42%
ST+4/V-3/V1	AGA	86	76	0.2006	0.0593	60%	52%
ST+4/V-3/V4	AGC	99	76	0.1960	0.0016	54%	40%
ST+4/V-1/V1	ACA	101	87	0.3833	0.0014	54%	42%
ST+4/V-1/V4	ACC	102	87	0.4317	0.0008	54%	41%
ST+4/V1/V4	AAC	102	87	0.3252	0.0013	55%	41%
ST+7/T1/V-4	GTC	106	68	0.0054	0.1502	53%	48%
ST+7/T1/V-3	GTG	98	68	0.0295	0.0658	43%	36%
ST+7/T1/V-1	GTC	89	53	0.0058	0.0743	74%	67%
ST+7/T1/V1	GTA	84	52	0.0177	0.0518	74%	67%
ST+7/T1/V4	GTC	97	58	0.0058	0.0289	64%	56%
ST+7/V-4/V-3	GCG	97	80	0.0783	0.1188	54%	47%
ST+7/V-4/V-1	GCC	92	68	0.0203	0.0934	65%	59%
ST+7/V-4/V1	GCA	90	68	0.0857	0.1003	65%	59%
ST+7/V-4/V4	GCC	94	74	0.2441	0.0392	56%	47%
ST+7/V-3/V-1	GGC	95	77	0.0626	0.0807	54%	47%
ST+7/V-3/V1	GGA	93	76	0.3285	0.0616	54%	47%
ST+7/V-3/V4	GGC	96	75	0.0766	0.0904	54%	47%
ST+7/V-1/V1	GCA	61	44	0.2511	0.0165	85%	78%
ST+7/V-1/V4	GCC	83	62	0.1579	0.0032	76%	66%
ST+7/V1/V4	GAC	82	61	0.1877	0.0050	76%	66%
T1/V-4/V-3	TCG	90	79	0.1410	0.6399	50%	52%
T1/V-4/V-3	TCA	46	36	0.1410	0.6812	12%	13%
T1/V-4/V-1	TCC	111	69	0.0014	0.3062	54%	50%
T1/V-4/V1	TCA	95	73	0.1714	0.7134	59%	61%
T1/V-4/V4	TCC	104	66	0.0217	0.6140	45%	43%

T1/V-3/V-1	TGC	105	71	0.0113	0.2080	42%	37%
T1/V-3/V1	TGA	96	76	0.2641	0.8990	48%	48%
T1/V-3/V4	TGC	105	69	0.0138	0.6748	42%	41%
T1/V-1/V1	TCA	76	45	0.0131	0.0390	81%	74%
T1/V-1/V4	TCC	97	59	0.0063	0.0146	71%	62%
T1/V1/V4	TAC	98	58	0.0035	0.0207	72%	63%
V-4/V-3/V-1	CGC	92	80	0.1065	0.1999	54%	48%
V-4/V-3/V-1	CAC	48	37	0.1065	0.7257	12%	12%
V-4/V-3/V1	CAA	45	39	0.8169	0.7142	12%	13%
V-4/V-3/V4	CGC	92	76	0.2275	0.5461	54%	52%
V-4/V-1/V1	CCA	90	69	0.0889	0.2305	65%	61%
V-4/V-1/V4	CCC	96	77	0.2412	0.0903	56%	49%
V-4/V1/V4	CAC	97	75	0.3730	0.1078	57%	50%
V-3/V-1/V1	GCA	97	81	0.2076	0.1888	54%	48%
V-3/V-1/V4	GCC	99	78	0.1115	0.1616	54%	48%
V-3/V1/V4	GAC	99	76	0.1093	0.1643	54%	48%
V-1/V1/V4	CAC	75	56	0.0973	0.0013	83%	73%
S1/T1/V-1/V1	GTCA	74	41	0.0053	0.0390	81%	74%
S1/T1/V-1/V4	GTCC	96	58	0.0051	0.0122	72%	62%
S1/T1/V1/V4	GTAC	97	58	0.0059	0.0182	72%	63%
S1/V-1/V1/V4	GCAC	75	56	0.1539	0.0011	83%	73%
S2/ST+7/T1/V-4	GGTC	102	62	0.0059	0.1211	53%	47%
S2/ST+7/T1/V-3	GGTG	93	59	0.0049	0.0960	42%	36%
S2/ST+7/T1/V-1	GGTC	92	48	0.0016	0.1038	72%	67%
S2/ST+7/T1/V4	GGTC	95	52	0.0031	0.0189	64%	55%
S2/ST+7/V-4/V-1	GGCC	106	66	0.0015	0.1972	53%	48%
S2/ST+7/V-4/V4	GGCC	95	59	0.0265	0.0340	45%	36%
S2/ST+7/V-3/V-1	GGGC	95	61	0.0021	0.0731	43%	36%
S2/ST+7/V-3/V4	GGGC	96	61	0.0075	0.0684	42%	36%
S2/ST+7/V-1/V4	GGCC	95	54	0.0017	0.0224	64%	55%
S2/T1/V-4/V-1	GTCC	105	62	0.0028	0.2782	54%	49%
S2/T1/V-4/V4	GTCC	98	57	0.0141	0.2564	44%	39%
S2/T1/V-3/V-1	GTGC	99	62	0.0087	0.2362	42%	37%
S2/T1/V-3/V4	GTGC	99	59	0.0081	0.2263	42%	37%
S2/T1/V-1/V4	GTCC	90	54	0.0133	0.0189	71%	62%
S2/V-4/V-1/V4	GCCC	98	61	0.0166	0.1085	45%	39%
S2/V-3/V-1/V4	GGCC	100	63	0.0111	0.1818	42%	37%
ST+7/T1/V-4/V-1	GTCC	108	68	0.0062	0.1381	53%	48%
ST+7/T1/V-4/V4	GTCC	99	62	0.0318	0.0851	44%	37%
ST+7/T1/V-3/V-1	GTGC	100	68	0.0222	0.0906	42%	36%
ST+7/T1/V-3/V4	GTGC	100	65	0.0138	0.1179	42%	36%
ST+7/T1/V-1/V4	GTCC	97	58	0.0071	0.0144	64%	55%
ST+7/V-4/V-1/V4	GCCC	94	74	0.1296	0.0304	56%	47%
ST+7/V-3/V-1/V4	GGCC	96	75	0.0825	0.0736	54%	47%
T1/V-4/V-1/V4	TCCC	103	64	0.0102	0.1670	44%	39%
T1/V-3/V-1/V4	TGCC	105	66	0.0081	0.1992	42%	37%
T1/V-1/V1/V4	TCAC	96	59	0.0029	0.0140	72%	62%
S1/T1/V-1/V1/V4	GTCAC	95	58	0.0111	0.0122	72%	62%
S2/ST+7/T1/V-3/V-1	GGTGC	95	59	0.0028	0.1002	42%	36%



S2/ST+7/T1/V-3/V4	GGTGC	95	58	0.0062	0.1055	42%	36%
S2/ST+7/T1/V-1/V4	GGTCC	95	52	0.0031	0.0208	64%	55%
S2/ST+7/V-3/V-1/V4	GGGCC	96	61	0.0114	0.0819	42%	36%
S2/T1/V-3/V-1/V4	GTGCC	99	59	0.0126	0.2204	42%	37%
ST+7/T1/V-3/V-1/V4	GTGCC	100	65	0.0176	0.0919	42%	36%

TABLE 28 (CON'T)

Asthma Yes/No UK							
SNP(s)	Over-Transmitted Allele or Haplo	T	NT	TDTP-value	Case/Cntl p-value	Case freq	Cntl freq
L-1	A	23	22	1.0000	0.1380	8%	13%
S1	G	30	11	0.0043	0.0260	95%	89%
S2	G	50	32	0.0598	0.0041	84%	73%
ST+4	A	75	73	0.9345	0.0191	59%	48%
ST+7	G	52	28	0.0097	0.0535	86%	80%
T1	T	26	19	0.3713	0.1473	91%	87%
V-4	G	59	54	0.7069	0.7529	27%	25%
V-3	A	65	60	0.7207	0.7032	40%	38%
V-1	C	36	17	0.0127	0.0105	94%	86%
V1	T	6	5	1.0000	0.7385	1%	2%
V4	C	61	40	0.0460	0.0328	84%	75%
L-1/S1	GG	47	26	0.0110	0.0031	87%	77%
L-1/S2	GG	55	32	0.0073	0.0060	84%	73%
L-1/ST+4	GC	71	68	0.9772	0.0942	41%	49%
L-1/ST+7	GG	67	40	0.0073	0.0062	78%	67%
L-1/T1	GT	24	19	0.1855	0.2007	91%	87%
L-1/V-4	GC	68	65	0.9154	0.5705	65%	62%
L-1/V-3	GA	66	64	0.9916	0.6691	40%	38%
L-1/V-1	GC	53	28	0.0038	0.0009	85%	74%
L-1/V1	GA	26	22	0.8253	0.0902	90%	85%
L-1/V4	GC	64	43	0.0866	0.0045	75%	63%
S1/S2	GG	53	29	0.0044	0.0037	84%	73%
S1/ST+4	GA	79	68	0.0599	0.0005	54%	39%
S1/ST+4	GC	73	66	0.0599	0.0478	41%	51%
S1/ST+7	GG	50	25	0.0037	0.0666	86%	80%
S1/T1	GT	52	25	0.0020	0.0046	87%	76%
S1/V-4	GC	69	52	0.0198	0.3178	68%	64%
S1/V-3	GG	74	61	0.0341	0.4179	55%	51%
S1/V-1	GC	36	16	0.0052	0.0080	94%	86%
S1/V1	GA	34	16	0.0104	0.0242	94%	87%
S1/V4	GC	60	42	0.0200	0.0286	83%	75%
S2/ST+4	GA	86	60	0.0774	0.0001	47%	28%
S2/ST+7	GG	73	40	0.0016	0.0124	76%	66%
S2/T1	GT	54	28	0.0070	0.0030	84%	72%

S2/V-4	GC	86	58	0.0230	0.0782	57%	49%
S2/V-3	GG	81	54	0.0231	0.0253	46%	36%
S2/V-1	GC	56	29	0.0038	0.0033	84%	73%
S2/V1	GA	52	29	0.0130	0.0032	84%	73%
S2/V4	GC	66	42	0.0189	0.0046	73%	61%
ST+4/ST+7	AG	88	65	0.0307	0.0008	55%	39%
ST+4/T1	AT	71	63	0.7750	0.0106	51%	38%
ST+4/V-4	AC	74	70	0.9448	0.0283	59%	48%
ST+4/V-3	AG	76	66	0.4005	0.0337	59%	48%
ST+4/V-1	AC	84	68	0.0872	0.0008	55%	39%
ST+4/V1	CA	71	68	0.9254	0.0354	39%	50%
ST+4/V4	AC	83	68	0.0857	0.0004	55%	37%
ST+7/T1	GT	67	34	0.0013	0.0060	78%	66%
ST+7/V-4	GC	84	60	0.0070	0.1297	67%	61%
ST+7/V-3	GG	89	61	0.0142	0.0921	56%	48%
ST+7/V-1	GC	54	29	0.0087	0.0670	86%	80%
ST+7/V1	GA	51	29	0.0201	0.0513	86%	80%
ST+7/V4	GC	72	44	0.0072	0.0553	75%	67%
T1/V-4	TC	65	58	0.4214	0.5411	65%	62%
T1/V-3	TG	68	62	0.8129	0.5856	51%	49%
T1/V-1	TC	59	31	0.0045	0.0011	85%	73%
T1/V1	TA	30	22	0.4868	0.0939	90%	85%
T1/V4	TC	73	44	0.0135	0.0060	75%	63%
V-4/V-3	CA	42	39	0.1812	0.9566	13%	13%
V-4/V-3	GG	6	0	0.1812	0.3735	1%	0%
V-4/V-1	CC	74	55	0.0161	0.2005	67%	61%
V-4/V1	GA	54	51	0.9242	0.6085	27%	25%
V-4/V4	CC	79	60	0.1113	0.1546	57%	50%
V-3/V-1	GC	80	64	0.0531	0.2704	54%	49%
V-3/V1	GA	65	64	1.0000	0.7729	58%	60%
V-3/V4	GC	80	60	0.0179	0.2300	55%	49%
V-1/V1	CA	36	19	0.0189	0.0080	94%	86%
V-1/V4	CC	63	42	0.0244	0.0058	83%	73%
V1/V4	AC	63	40	0.0295	0.0088	84%	74%
L-1/S1/S2	GGG	49	28	0.0162	0.0054	84%	73%
L-1/S1/ST+4	GGA	67	53	0.1150	0.0002	46%	29%
L-1/S1/ST+7	GGG	58	33	0.0093	0.0087	78%	67%
L-1/S1/T1	GGT	45	24	0.0092	0.0106	86%	76%
L-1/S1/V-4	GGC	73	51	0.0421	0.0704	60%	52%
L-1/S1/V-3	GGG	67	55	0.0991	0.0706	47%	39%
L-1/S1/V-1	GGC	51	27	0.0106	0.0012	86%	74%
L-1/S1/V1	GGA	48	27	0.0202	0.0038	86%	75%
L-1/S1/V4	GGC	63	44	0.0348	0.0072	75%	64%
L-1/S2/ST+4	GGA	73	50	0.0384	0.0001	46%	28%
L-1/S2/ST+7	GGG	67	37	0.0025	0.0175	76%	66%
L-1/S2/T1	GGT	49	25	0.0050	0.0050	83%	73%
L-1/S2/V-4	GGC	79	53	0.0244	0.0880	57%	48%
L-1/S2/V-3	GGG	72	50	0.0281	0.0244	46%	35%
L-1/S2/V-1	GGC	52	28	0.0062	0.0057	84%	73%

L-1/S2/V1	GGA	50	28	0.0206	0.0055	84%	73%
L-1/S2/V4	GGC	59	40	0.0739	0.0022	74%	61%
L-1/ST+4/ST+7	GAG	75	54	0.0475	0.0001	47%	29%
L-1/ST+4/T1	GCT	61	58	0.3595	0.1053	41%	49%
L-1/ST+4/T1	GAT	60	57	0.3595	0.0125	50%	38%
L-1/ST+4/V-4	GAC	69	63	0.9795	0.0091	51%	38%
L-1/ST+4/V-3	GAG	65	60	0.8503	0.0092	50%	38%
L-1/ST+4/V-1	GAC	70	54	0.0624	0.0002	47%	28%
L-1/ST+4/V1	GCA	63	58	0.9342	0.1331	39%	47%
L-1/ST+4/V4	GAC	70	52	0.0641	0.0002	46%	28%
L-1/ST+7/T1	GGT	60	30	0.0004	0.0092	77%	67%
L-1/ST+7/V-4	GGC	84	58	0.0163	0.0225	59%	48%
L-1/ST+7/V-3	GGG	79	53	0.0094	0.0083	47%	35%
L-1/ST+7/V-1	GGC	62	34	0.0030	0.0055	78%	67%
L-1/ST+7/V1	GGA	59	34	0.0126	0.0040	78%	67%
L-1/ST+7/V4	GGC	71	43	0.0124	0.0168	66%	55%
L-1/T1/V-4	GTC	61	54	0.1733	0.6074	64%	62%
L-1/T1/V-3	GTA	57	53	0.2005	0.6792	40%	38%
L-1/T1/V-1	GTC	51	24	0.0017	0.0026	85%	73%
L-1/T1/V1	GTA	26	19	0.3016	0.1243	89%	85%
L-1/T1/V4	GTC	63	41	0.0478	0.0115	75%	64%
L-1/V-4/V-3	GCA	40	34	0.3154	0.9681	13%	13%
L-1/V-4/V-3	GGG	5	0	0.3154	1.0000	0%	0%
L-1/V-4/V-1	GCC	77	52	0.0177	0.0383	59%	49%
L-1/V-4/V1	GCA	64	59	0.9321	0.5449	64%	60%
L-1/V-4/V4	GCC	73	48	0.0996	0.0500	49%	39%
L-1/V-3/V-1	GGC	70	53	0.0197	0.0366	46%	36%
L-1/V-3/V1	GAA	59	55	0.9284	0.6816	40%	38%
L-1/V-3/V4	GGC	71	52	0.0489	0.0697	47%	38%
L-1/V-1/V1	GCA	51	28	0.0091	0.0009	86%	74%
L-1/V-1/V4	GCC	66	43	0.0362	0.0023	75%	62%
L-1/V1/V4	GAC	66	42	0.0465	0.0013	75%	62%
S1/S2/ST+4	GGA	75	54	0.0635	0.0003	46%	29%
S1/S2/ST+7	GGG	65	32	0.0021	0.0120	76%	66%
S1/S2/T1	GGT	52	28	0.0084	0.0031	84%	72%
S1/S2/V-4	GGC	79	52	0.0173	0.0916	57%	49%
S1/S2/V-3	GGG	72	51	0.0342	0.0318	46%	36%
S1/S2/V-1	GGC	54	29	0.0071	0.0033	84%	73%
S1/S2/V1	GGA	51	29	0.0119	0.0039	84%	73%
S1/S2/V4	GGC	65	42	0.0075	0.0110	73%	61%
S1/ST+4/ST+7	GAG	73	61	0.0435	0.0016	54%	39%
S1/ST+4/ST+7	GCG	60	47	0.0435	0.0391	31%	41%
S1/ST+4/T1	GAT	77	56	0.0469	0.0002	46%	28%
S1/ST+4/V-4	GAC	76	60	0.0972	0.0013	54%	39%
S1/ST+4/V-3	GAG	76	57	0.0571	0.0015	54%	39%
S1/ST+4/V-1	GAC	80	67	0.1247	0.0009	54%	38%
S1/ST+4/V1	GAA	78	68	0.1194	0.0003	54%	39%
S1/ST+4/V1	GCA	72	65	0.1194	0.0632	39%	48%
S1/ST+4/V4	GAC	80	69	0.1119	0.0007	54%	38%

S1/ST+7/T1	GGT	64	30	0.0009	0.0087	77%	66%
S1/ST+7/V-4	GGC	72	52	0.0206	0.1457	67%	61%
S1/ST+7/V-3	GGG	75	56	0.0203	0.1689	55%	48%
S1/ST+7/V-1	GGC	51	25	0.0048	0.0650	86%	80%
S1/ST+7/V1	GGA	48	25	0.0143	0.0641	86%	80%
S1/ST+7/V4	GGC	70	44	0.0138	0.0848	74%	67%
S1/T1/V-4	GTC	78	52	0.0096	0.0617	60%	51%
S1/T1/V-3	GTG	75	55	0.0318	0.0660	47%	38%
S1/T1/V-1	GTC	56	27	0.0015	0.0014	85%	73%
S1/T1/V1	GTA	53	27	0.0046	0.0048	85%	74%
S1/T1/V4	GTC	72	45	0.0039	0.0096	74%	63%
S1/V-4/V-3	GCG	73	61	0.0288	0.3543	56%	51%
S1/V-4/V-1	GCC	72	53	0.0272	0.3112	67%	62%
S1/V-4/V1	GCA	70	53	0.0402	0.3481	67%	63%
S1/V-4/V4	GCC	78	61	0.0383	0.1595	56%	50%
S1/V-3/V-1	GGC	77	61	0.0268	0.2808	54%	49%
S1/V-3/V1	GGA	75	60	0.0538	0.3642	54%	49%
S1/V-3/V4	GGC	78	61	0.0281	0.3423	55%	50%
S1/V-1/V1	GCA	34	16	0.0093	0.0101	94%	86%
S1/V-1/V4	GCC	62	42	0.0180	0.0061	83%	73%
S1/V1/V4	GAC	62	41	0.0165	0.0080	83%	73%
S2/ST+4/ST+7	GAG	79	54	0.0659	0.0001	47%	29%
S2/ST+4/T1	GAT	76	51	0.0867	0.0001	46%	28%
S2/ST+4/V-4	GAC	80	50	0.0892	0.0001	46%	28%
S2/ST+4/V-3	GAG	79	48	0.0432	0.0001	46%	28%
S2/ST+4/V-1	GAC	79	52	0.0279	0.0001	47%	28%
S2/ST+4/V1	GAA	77	54	0.0724	0.0001	46%	29%
S2/ST+4/V4	GAC	78	53	0.0949	0.0001	46%	28%
S2/ST+7/T1	GGT	67	30	0.0002	0.0135	76%	66%
S2/ST+7/V-4	GGC	86	58	0.0082	0.0227	58%	47%
S2/ST+7/V-3	GGG	81	50	0.0056	0.0170	46%	34%
S2/ST+7/V-1	GGC	69	32	0.0003	0.0133	76%	66%
S2/ST+7/V1	GGA	66	32	0.0009	0.0107	77%	66%
S2/ST+7/V4	GGC	75	39	0.0013	0.0147	66%	54%
S2/T1/V-4	GTC	78	48	0.0124	0.0706	57%	48%
S2/T1/V-3	GTG	74	48	0.0257	0.0258	46%	35%
S2/T1/V-1	GTC	55	28	0.0043	0.0027	84%	73%
S2/T1/V1	GTA	52	28	0.0174	0.0036	84%	72%
S2/T1/V4	GTC	65	40	0.0424	0.0042	74%	61%
S2/V-4/V-3	GCG	77	54	0.0223	0.0273	46%	35%
S2/V-4/V-1	GCC	82	52	0.0082	0.0501	58%	48%
S2/V-4/V1	GCA	79	52	0.0281	0.0736	57%	49%
S2/V-4/V4	GCC	77	48	0.0206	0.0439	47%	37%
S2/V-3/V-1	GGC	76	51	0.0136	0.0287	46%	36%
S2/V-3/V1	GGA	74	51	0.0698	0.0277	46%	36%
S2/V-3/V4	GGC	77	49	0.0144	0.0344	46%	36%
S2/V-1/V1	GCA	54	29	0.0072	0.0040	84%	73%
S2/V-1/V4	GCC	66	42	0.0308	0.0059	73%	61%
S2/V1/V4	GAC	65	42	0.0087	0.0056	74%	61%

ST+4/ST+7/T1	AGT	74	52	0.0146	0.0001	47%	29%
ST+4/ST+7/T1	CGT	61	49	0.0146	0.1426	31%	38%
ST+4/ST+7/V-4	AGC	82	61	0.0680	0.0007	55%	39%
ST+4/ST+7/V-3	AGG	83	58	0.0216	0.0006	55%	38%
ST+4/ST+7/V-1	AGC	77	62	0.0643	0.0012	55%	39%
ST+4/ST+7/V-1	CGC	61	50	0.0643	0.0413	31%	40%
ST+4/ST+7/V1	AGA	75	61	0.1171	0.0006	55%	39%
ST+4/ST+7/V1	CGA	59	50	0.1171	0.0390	31%	41%
ST+4/ST+7/V4	AGC	78	62	0.0453	0.0015	54%	39%
ST+4/ST+7/V4	CGC	49	39	0.0453	0.0687	20%	28%
ST+4/T1/V-4	ATC	66	57	0.7439	0.0085	51%	38%
ST+4/T1/V-3	ATG	67	53	0.4142	0.0083	50%	37%
ST+4/T1/V-1	ATC	82	56	0.0363	0.0001	46%	28%
ST+4/T1/V1	ATA	70	64	0.8628	0.0113	51%	38%
ST+4/T1/V4	ATC	80	55	0.0555	0.0002	46%	28%
ST+4/V-4/V-3	ACG	70	65	0.1452	0.0412	58%	48%
ST+4/V-4/V-1	ACC	80	61	0.0526	0.0004	55%	39%
ST+4/V-4/V1	CGA	52	50	0.9954	0.6899	27%	25%
ST+4/V-4/V4	ACC	79	58	0.0706	0.0004	54%	37%
ST+4/V-3/V-1	AGC	80	58	0.0611	0.0015	54%	39%
ST+4/V-3/V1	AGA	68	60	0.3132	0.0368	59%	49%
ST+4/V-3/V4	AGC	81	57	0.0381	0.0006	54%	37%
ST+4/V-1/V1	ACA	82	67	0.0940	0.0011	54%	39%
ST+4/V-1/V4	ACC	83	67	0.0952	0.0006	55%	38%
ST+4/V1/V4	AAC	83	67	0.0794	0.0002	55%	37%
ST+7/T1/V-4	GTC	81	51	0.0008	0.0175	59%	47%
ST+7/T1/V-3	GTG	77	51	0.0081	0.0069	47%	34%
ST+7/T1/V-1	GTC	68	34	0.0024	0.0060	77%	66%
ST+7/T1/V1	GTA	64	34	0.0043	0.0045	78%	66%
ST+7/T1/V4	GTC	78	40	0.0005	0.0227	66%	55%
ST+7/V-4/V-3	GCG	83	61	0.0037	0.1856	55%	48%
ST+7/V-4/V-1	GCC	76	53	0.0049	0.1265	67%	60%
ST+7/V-4/V1	GCA	74	53	0.0107	0.1410	67%	61%
ST+7/V-4/V4	GCC	78	56	0.0231	0.0681	56%	47%
ST+7/V-3/V-1	GGC	80	58	0.0135	0.1666	54%	48%
ST+7/V-3/V1	GGA	78	57	0.0443	0.1035	55%	47%
ST+7/V-3/V4	GGC	81	56	0.0081	0.1874	54%	48%
ST+7/V-1/V1	GCA	52	29	0.0237	0.0663	86%	80%
ST+7/V-1/V4	GCC	72	44	0.0114	0.0243	75%	66%
ST+7/V1/V4	GAC	71	43	0.0111	0.0574	75%	67%
T1/V-4/V-3	TCA	38	32	0.4051	0.9715	13%	13%
T1/V-4/V-1	TCC	83	52	0.0014	0.0267	58%	48%
T1/V-4/V1	TCA	65	58	0.6189	0.4923	63%	60%
T1/V-4/V4	TCC	79	50	0.0281	0.0442	48%	39%
T1/V-3/V-1	TGC	79	54	0.0263	0.0331	45%	35%
T1/V-3/V1	TGA	67	59	0.8777	0.4892	50%	46%
T1/V-3/V4	TGC	79	52	0.0133	0.0681	46%	37%
T1/V-1/V1	TCA	55	30	0.0081	0.0011	85%	73%
T1/V-1/V4	TCC	74	43	0.0031	0.0038	74%	62%

T1/V1/V4	TAC	74	42	0.0055	0.0012	75%	61%
V-4/V-3/V-1	CGC	76	62	0.0155	0.2083	54%	48%
V-4/V-3/V1	CAA	37	35	0.6465	0.9865	13%	13%
V-4/V-3/V4	CGC	76	58	0.0226	0.2824	54%	49%
V-4/V-1/V1	CCA	73	54	0.0167	0.2373	67%	62%
V-4/V-1/V4	CCC	79	59	0.0398	0.0744	56%	48%
V-4/V1/V4	CAC	79	57	0.0998	0.1000	57%	49%
V-3/V-1/V1	GCA	79	62	0.0658	0.2831	54%	49%
V-3/V-1/V4	GCC	81	59	0.0191	0.2312	54%	48%
V-3/V1/V4	GAC	81	57	0.0097	0.1462	55%	47%
V-1/V1/V4	CAC	62	41	0.0066	0.0088	83%	73%
S1/T1/V-1/V1	GTCA	53	27	0.0040	0.0008	85%	73%
S1/T1/V-1/V4	GTCC	73	43	0.0031	0.0027	74%	61%
S1/T1/V1/V4	GTAC	73	43	0.0029	0.0027	74%	62%
S1/V-1/V1/V4	GCAC	61	41	0.0180	0.0076	83%	73%
S2/ST+7/T1/V-4	GGTC	79	48	0.0018	0.0142	58%	46%
S2/ST+7/T1/V-3	GGTG	74	45	0.0022	0.0193	45%	35%
S2/ST+7/T1/V-1	GGTC	68	30	0.0003	0.0118	76%	66%
S2/ST+7/T1/V4	GGTC	74	36	0.0004	0.0095	66%	54%
S2/ST+7/V-4/V-1	GGCC	83	52	0.0030	0.0250	58%	47%
S2/ST+7/V-4/V4	GGCC	76	46	0.0096	0.0079	49%	35%
S2/ST+7/V-3/V-1	GGGC	76	47	0.0040	0.0180	46%	35%
S2/ST+7/V-3/V4	GGGC	77	47	0.0063	0.0124	46%	34%
S2/ST+7/V1/V4	GGCC	75	39	0.0009	0.0115	66%	54%
S2/T1/V-4/V-1	GTCC	79	48	0.0027	0.0265	58%	48%
S2/T1/V-4/V4	GTCC	75	44	0.0192	0.0412	47%	37%
S2/T1/V-3/V-1	GTGC	75	48	0.0052	0.0347	45%	35%
S2/T1/V-3/V4	GTGC	75	45	0.0179	0.0371	45%	36%
S2/T1/V-1/V4	GTCC	65	40	0.0328	0.0029	74%	61%
S2/V-4/V-1/V4	GCCC	77	48	0.0325	0.0145	49%	37%
S2/V-3/V-1/V4	GGCC	77	49	0.0280	0.0463	45%	36%
ST+7/T1/V-4/V-1	GTCC	82	51	0.0014	0.0152	58%	47%
ST+7/T1/V-4/V4	GTCC	77	46	0.0042	0.0166	47%	36%
ST+7/T1/V-3/V-1	GTGC	78	51	0.0117	0.0140	45%	34%
ST+7/T1/V-3/V4	GTGC	78	48	0.0044	0.0202	45%	35%
ST+7/T1/V-1/V4	GTCC	78	40	0.0024	0.0070	67%	54%
ST+7/V-4/V-1/V4	GCCC	78	56	0.0207	0.0446	57%	47%
ST+7/V-3/V-1/V4	GGCC	81	56	0.0111	0.1588	54%	47%
T1/V-4/V-1/V4	TCCC	79	48	0.0072	0.0214	48%	36%
T1/V-3/V-1/V4	TGCC	79	49	0.0067	0.0357	45%	35%
T1/V-1/V1/V4	TCAC	73	43	0.0004	0.0038	74%	62%
S1/T1/V-1/V1/V4	GTAC	72	43	0.0008	0.0021	74%	62%
S2/ST+7/T1/V-3/V-1	GGTGC	75	45	0.0003	0.0205	45%	35%
S2/ST+7/T1/V-3/V4	GGTGC	75	44	0.0014	0.0201	45%	35%
S2/ST+7/T1/V-1/V4	GGTCC	74	36	0.0005	0.0087	66%	54%
S2/ST+7/V-3/V-1/V4	GGGCC	77	47	0.0135	0.0134	46%	35%
S2/T1/V-3/V-1/V4	GTGCC	75	45	0.0161	0.0399	45%	36%
ST+7/T1/V-3/V-1/V4	GTGCC	78	48	0.0063	0.0176	45%	34%

**TABLE 28 (CON'T)**

Asthma Yes/No US							
SNP(s)	Over- Transmitted Allele or Haplo	T	NT	TD p-value	Case/ Cntl p-value	Case freq	Cntl freq
L-1	G	15	8	0.2100	0.0116	78%	92%
S1	A	9	7	0.8036	0.7873	8%	10%
S2	G	23	10	0.0351	0.1571	65%	75%
ST+4	C	20	18	0.8714	0.5150	37%	43%
ST+7	A	13	7	0.2632	0.3413	17%	24%
T1	T	17	8	0.1078	0.0030	76%	92%
V-4	C	14	10	0.5413	0.5795	72%	77%
V-3	A	18	16	0.8642	0.8684	33%	35%
V-1	A	10	7	0.6291	0.5262	13%	17%
V1	A	2	1	1.0000	0.7308	96%	94%
V4	G	15	12	0.7011	0.5583	17%	21%
L-1/S1	GG	17	12	0.2469	0.1892	72%	82%
L-1/S2	GG	23	14	0.1994	0.1562	65%	75%
L-1/ST+4	GA	28	20	0.2176	0.3061	41%	49%
L-1/ST+7	GA	15	7	0.1592	0.2677	17%	24%
L-1/T1	GT	16	8	0.1677	0.0033	76%	92%
L-1/V-4	GC	30	16	0.0763	0.0071	50%	69%
L-1/V-3	GG	27	19	0.2133	0.1469	44%	57%
L-1/V-1	GC	18	14	0.2369	0.1660	65%	75%
L-1/V1	GA	10	6	0.2369	0.5475	13%	17%
L-1/V1	GA	17	8	0.1204	0.0486	74%	86%
L-1/V4	GC	20	15	0.3011	0.1752	61%	71%
S1/S2	GG	21	11	0.0422	0.1431	65%	75%
S1/ST+4	AA	9	7	0.8773	0.5743	8%	10%
S1/ST+7	AA	9	6	0.2857	0.9946	10%	10%
S1/ST+7	GA	7	3	0.2857	0.1514	7%	14%
S1/T1	GT	20	13	0.2095	0.1095	70%	82%
S1/V-4	GC	19	16	0.6136	0.7811	64%	67%
S1/V-3	AG	8	6	0.9435	0.6472	8%	10%
S1/V-1	AA	9	5	0.5677	1.0000	10%	10%
S1/V1	AA	9	7	0.8527	0.5640	8%	10%
S1/V4	AG	9	6	0.7652	0.9978	10%	10%
S2/ST+4	GA	26	17	0.3120	0.4193	30%	36%
S2/ST+7	GG	22	16	0.0248	0.3353	61%	68%
S2/ST+7	CA	11	7	0.0248	0.4560	13%	17%
S2/ST+7	GA	7	3	0.0248	0.4883	4%	7%
S2/T1	GT	24	14	0.2315	0.1083	63%	75%
S2/V-4	GC	28	15	0.0684	0.0304	37%	52%
S2/V-3	GG	24	16	0.1690	0.2245	31%	40%
S2/V-1	GC	21	11	0.0106	0.1648	65%	75%
S2/V1	GA	22	11	0.0624	0.1645	65%	75%

S2/V4	GC	24	12	0.0165	0.8376	63%	64%
ST+4/ST+7	AA	10	6	0.3518	0.5418	10%	14%
ST+4/ST+7	CA	8	3	0.3518	0.4565	7%	10%
ST+4/T1	AT	30	19	0.1548	0.1835	39%	49%
ST+4/V-4	CC	13	6	0.2718	0.0788	10%	20%
ST+4/V-3	CA	20	19	1.0000	0.8415	33%	35%
ST+4/V-1	AA	9	5	0.7672	0.6114	10%	13%
ST+4/V1	AA	20	18	0.9025	0.4532	64%	57%
ST+4/V4	AG	9	6	0.8877	0.9129	10%	10%
ST+7/T1	AT	14	7	0.1886	0.2593	17%	24%
ST+7/V-4	AC	12	6	0.2223	0.3209	14%	21%
ST+7/V-3	AG	12	6	0.3409	0.3257	13%	19%
ST+7/V-1	AA	10	6	0.3358	0.5349	13%	17%
ST+7/V-1	AC	6	3	0.3358	0.3852	4%	7%
ST+7/V1	AA	14	7	0.2577	0.4406	13%	18%
ST+7/V4	AG	10	7	0.4163	0.4395	15%	10%
ST+7/V4	AC	7	3	0.4163	0.0120	2%	14%
T1/V-4	TC	30	16	0.0612	0.0053	48%	69%
T1/V-3	TG	29	18	0.1036	0.0893	43%	57%
T1/V-1	TC	21	15	0.2153	0.1267	63%	75%
T1/V1	TA	19	9	0.0969	0.0223	72%	86%
T1/V4	TC	24	16	0.1748	0.1403	59%	71%
V-4/V-3	CA	10	4	0.3196	0.1936	6%	12%
V-4/V-1	CC	17	15	0.6156	0.8955	59%	60%
V-4/V-1	CA	10	7	0.6156	0.4901	13%	17%
V-4/V1	CA	16	10	0.4921	0.7697	69%	71%
V-4/V4	CG	15	10	0.6228	0.7499	17%	19%
V-3/V-1	GA	9	7	0.9452	0.4930	13%	17%
V-3/V1	GA	18	16	0.8979	0.6003	63%	59%
V-3/V4	GG	10	7	0.9233	0.5752	14%	10%
V-1/V1	AA	9	5	0.5689	0.7650	9%	11%
V-1/V4	AG	10	7	0.8532	0.5024	13%	10%
V1/V4	AG	14	12	0.8827	0.2048	13%	21%
L-1/S1/S2	GGG	21	13	0.1353	0.1615	65%	75%
L-1/S1/ST+4	GGA	23	17	0.3377	0.3922	33%	39%
L-1/S1/ST+7	GAA	9	5	0.2884	0.7508	9%	10%
L-1/S1/ST+7	GGA	7	3	0.2884	0.1709	7%	14%
L-1/S1/T1	GGT	18	13	0.3740	0.1225	70%	82%
L-1/S1/V-4	GGC	26	17	0.2543	0.0264	42%	59%
L-1/S1/V-3	GGG	22	17	0.3697	0.2224	36%	47%
L-1/S1/V-1	GGC	18	13	0.1949	0.1828	65%	75%
L-1/S1/V-1	GAA	9	4	0.1949	0.9559	10%	10%
L-1/S1/V1	GGA	19	13	0.2846	0.3498	69%	76%
L-1/S1/V4	GGC	20	14	0.2726	0.2516	62%	71%
L-1/S2/ST+4	GGA	23	17	0.4714	0.4109	30%	36%
L-1/S2/ST+7	GGG	22	18	0.0512	0.3738	61%	68%
L-1/S2/ST+7	GCA	11	6	0.0512	0.5492	13%	17%
L-1/S2/ST+7	GGA	7	3	0.0512	0.4350	4%	7%
L-1/S2/T1	GGT	22	14	0.3930	0.1339	63%	75%



L-1/S2/V-4	GGC	26	15	0.1452	0.0298	37%	52%
L-1/S2/V-3	GGG	21	16	0.2228	0.2277	31%	40%
L-1/S2/V-1	GGC	21	13	0.0206	0.1484	65%	75%
L-1/S2/V1	GGA	22	13	0.1990	0.1581	65%	75%
L-1/S2/V4	GGC	22	13	0.0358	0.7429	62%	64%
L-1/ST+4/ST+7	GAG	22	18	0.2357	0.5054	30%	35%
L-1/ST+4/ST+7	GAA	10	5	0.2357	0.5672	10%	14%
L-1/ST+4/ST+7	GCA	8	4	0.2357	0.4259	6%	10%
L-1/ST+4/T1	GAT	27	18	0.3306	0.1871	39%	49%
L-1/ST+4/V-4	GAC	26	18	0.2263	0.2453	40%	49%
L-1/ST+4/V-4	GCC	12	6	0.2263	0.0924	10%	20%
L-1/ST+4/V-3	GAG	26	18	0.3009	0.2456	41%	49%
L-1/ST+4/V-1	GAC	23	18	0.3345	0.4090	30%	36%
L-1/ST+4/V-1	GAA	9	4	0.3345	0.6342	10%	13%
L-1/ST+4/V1	GAA	27	18	0.2911	0.3194	41%	49%
L-1/ST+4/V4	GAC	23	18	0.4359	0.3199	31%	39%
L-1/ST+4/V4	GAG	9	5	0.4359	0.8722	9%	10%
L-1/ST+7/T1	GAT	14	6	0.2291	0.2644	17%	24%
L-1/ST+7/V-4	GGC	23	17	0.1444	0.0474	36%	49%
L-1/ST+7/V-4	GAC	12	5	0.1444	0.3844	15%	20%
L-1/ST+7/V-3	GGG	20	17	0.2350	0.3482	31%	38%
L-1/ST+7/V-3	GAG	12	5	0.2350	0.3831	13%	19%
L-1/ST+7/V-1	GAA	10	5	0.2786	0.5280	13%	17%
L-1/ST+7/V1	GAA	14	6	0.2436	0.4738	13%	18%
L-1/ST+7/V4	GAG	10	6	0.4151	0.4588	15%	10%
L-1/ST+7/V4	GAC	7	3	0.4151	0.0112	2%	14%
L-1/T1/V-4	GTC	28	15	0.0966	0.0056	48%	69%
L-1/T1/V-3	GTG	26	17	0.2203	0.0905	43%	57%
L-1/T1/V-1	GTC	19	15	0.3430	0.1255	63%	75%
L-1/T1/V-1	GTA	10	6	0.3430	0.5480	13%	17%
L-1/T1/V1	GTA	18	9	0.1789	0.0211	72%	86%
L-1/T1/V4	GTC	21	16	0.4009	0.1375	59%	71%
L-1/V-4/V-3	GCG	27	18	0.1983	0.1259	44%	57%
L-1/V-4/V-1	GCC	25	17	0.2524	0.0320	37%	52%
L-1/V-4/V1	GCA	27	14	0.1329	0.0215	46%	63%
L-1/V-4/V4	GCC	23	16	0.2898	0.0373	33%	50%
L-1/V-4/V4	GCG	14	9	0.2898	0.7018	17%	19%
L-1/V-3/V-1	GGC	22	17	0.3747	0.2308	31%	40%
L-1/V-3/V1	GGA	25	16	0.2682	0.1738	41%	51%
L-1/V-3/V4	GGC	22	17	0.4343	0.0785	32%	46%
L-1/V-3/V4	GGG	10	6	0.4343	0.7467	12%	10%
L-1/V-1/V1	GCA	18	14	0.2423	0.2204	66%	75%
L-1/V-1/V1	GAA	9	4	0.2423	0.6250	8%	11%
L-1/V-1/V4	GCC	19	15	0.3549	0.7760	62%	64%
L-1/V-1/V4	GAG	10	6	0.3549	0.5564	13%	10%
L-1/V1/V4	GAC	20	15	0.3308	0.7936	63%	65%
L-1/V1/V4	GAG	13	9	0.3308	0.1248	11%	21%
S1/S2/ST+4	GGA	24	15	0.1432	0.3823	30%	36%
S1/S2/ST+7	GGG	21	16	0.0717	0.2756	60%	68%

S1/S2/ST+7	GGA	7	2	0.0717	0.6466	5%	7%
S1/S2/T1	GGT	24	14	0.1397	0.1085	63%	75%
S1/S2/V-4	GGC	25	14	0.0724	0.0298	37%	52%
S1/S2/V-3	GGG	22	14	0.1099	0.2261	31%	40%
S1/S2/V-1	GGC	21	11	0.0203	0.1688	65%	75%
S1/S2/V1	GGA	22	11	0.0246	0.1501	65%	75%
S1/S2/V4	GGC	24	12	0.0291	0.8506	62%	64%
S1/ST+4/ST+7	AAA	9	6	0.5566	0.8515	9%	10%
S1/ST+4/ST+7	GCA	7	3	0.5566	0.2862	7%	13%
S1/ST+4/T1	GAT	26	17	0.2445	0.2280	31%	39%
S1/ST+4/V-4	GCC	10	6	0.6103	0.0747	10%	20%
S1/ST+4/V-4	AAC	9	7	0.6103	0.5982	8%	10%
S1/ST+4/V-3	AAG	8	6	0.9462	0.5966	8%	10%
S1/ST+4/V-1	AAA	9	5	0.7679	0.8117	9%	10%
S1/ST+4/V1	AAA	9	7	0.9614	0.5950	8%	10%
S1/ST+4/V4	AAG	9	6	0.9014	0.9430	9%	10%
S1/ST+7/T1	GGT	20	18	0.2855	0.2791	59%	68%
S1/ST+7/T1	AAT	9	6	0.2855	0.9457	10%	10%
S1/ST+7/T1	GAT	7	3	0.2855	0.1676	7%	14%
S1/ST+7/V-4	AAC	9	6	0.5193	0.9985	10%	10%
S1/ST+7/V-4	GAG	5	2	0.5193	0.7922	3%	4%
S1/ST+7/V-3	AAG	9	5	0.7156	0.9995	10%	10%
S1/ST+7/V-3	GAA	5	2	0.7156	0.7489	4%	5%
S1/ST+7/V-1	AAA	9	5	0.5519	0.9959	10%	10%
S1/ST+7/V-1	GAC	6	3	0.5519	0.4170	4%	7%
S1/ST+7/V1	AAA	9	6	0.5113	0.6734	9%	10%
S1/ST+7/V1	GAA	7	3	0.5113	0.4611	4%	7%
S1/ST+7/V4	AAG	9	6	0.6409	0.9932	10%	10%
S1/ST+7/V4	GAC	7	3	0.6409	0.0091	2%	14%
S1/T1/V-4	GTC	29	17	0.1417	0.0158	40%	59%
S1/T1/V-3	GTG	26	17	0.1935	0.1477	34%	47%
S1/T1/V-1	GTC	21	14	0.1952	0.1230	63%	75%
S1/T1/V-1	ATA	9	5	0.1952	0.9968	10%	10%
S1/T1/V1	GTA	22	14	0.2347	0.2219	66%	76%
S1/T1/V4	GTC	24	15	0.2065	0.1627	59%	71%
S1/V-4/V-3	ACG	9	6	0.5762	0.6486	8%	10%
S1/V-4/V-3	GCA	8	4	0.5762	0.2068	6%	12%
S1/V-4/V-1	GCC	18	15	0.5920	0.8910	59%	60%
S1/V-4/V-1	ACA	9	5	0.5920	0.9951	10%	10%
S1/V-4/V1	GCA	19	15	0.6696	0.9796	61%	61%
S1/V-4/V4	ACG	9	6	0.7895	0.9938	10%	10%
S1/V-3/V-1	AGA	8	5	0.8714	0.9968	10%	10%
S1/V-3/V1	AGA	8	6	0.9569	0.6054	8%	10%
S1/V-3/V4	AGG	9	5	0.8646	0.9878	10%	10%
S1/V-1/V1	AAA	9	5	0.5715	0.8455	9%	10%
S1/V-1/V4	AAG	9	5	0.7404	0.9922	10%	10%
S1/V1/V4	AAG	9	6	0.8729	0.8360	9%	10%
S2/ST+4/ST+7	GAG	21	15	0.0948	0.3700	30%	36%
S2/ST+4/ST+7	CAA	10	6	0.0948	0.5948	11%	14%

S2/ST+4/ST+7	GCA	7	3	0.0948	0.4933	4%	7%
S2/ST+4/T1	GAT	24	15	0.3322	0.2640	28%	36%
S2/ST+4/V-4	GAC	22	15	0.2518	0.3938	30%	37%
S2/ST+4/V-4	GCC	11	5	0.2518	0.1070	7%	16%
S2/ST+4/V-3	GAG	25	16	0.1517	0.3763	31%	38%
S2/ST+4/V-3	GCA	21	17	0.1517	0.8580	33%	35%
S2/ST+4/V-1	GAC	24	15	0.0724	0.4121	30%	36%
S2/ST+4/V-1	CAA	9	5	0.0724	0.6096	10%	13%
S2/ST+4/V1	GAA	24	15	0.2030	0.3225	31%	38%
S2/ST+4/V4	GAC	24	15	0.1076	0.4569	31%	36%
S2/ST+4/V4	GCC	16	12	0.1076	0.6753	32%	29%
S2/ST+4/V4	CAG	9	6	0.1076	0.8373	11%	10%
S2/ST+7/T1	GGT	23	18	0.0604	0.2365	59%	68%
S2/ST+7/T1	CAT	10	7	0.0604	0.5339	13%	17%
S2/ST+7/T1	GAT	7	2	0.0604	0.3623	4%	7%
S2/ST+7/V-4	GGC	23	14	0.0346	0.0874	37%	49%
S2/ST+7/V-4	CAC	12	7	0.0346	0.4962	13%	18%
S2/ST+7/V-4	GAG	5	2	0.0346	0.9553	4%	4%
S2/ST+7/V-3	GGG	19	14	0.0631	0.3659	31%	38%
S2/ST+7/V-3	CAG	12	6	0.0631	0.4882	13%	18%
S2/ST+7/V-3	GAA	5	2	0.0631	0.8498	4%	4%
S2/ST+7/V-1	GGC	22	16	0.0270	0.3777	61%	68%
S2/ST+7/V-1	CAA	10	6	0.0270	0.4672	13%	17%
S2/ST+7/V-1	GAC	6	2	0.0270	0.4398	4%	7%
S2/ST+7/V1	GGA	22	16	0.0404	0.3461	61%	68%
S2/ST+7/V1	CAA	9	6	0.0404	0.6877	9%	11%
S2/ST+7/V1	GAA	7	2	0.0404	0.4380	4%	7%
S2/ST+7/V4	GGC	20	15	0.0549	0.6225	61%	57%
S2/ST+7/V4	CAG	10	7	0.0549	0.5174	13%	10%
S2/ST+7/V4	GAC	7	2	0.0549	0.2109	2%	7%
S2/T1/V-4	GTC	26	14	0.1220	0.0169	35%	52%
S2/T1/V-3	GTG	23	14	0.1421	0.1383	29%	40%
S2/T1/V-1	GTC	24	14	0.0265	0.1229	63%	75%
S2/T1/V-1	CTA	10	5	0.0265	0.4877	13%	17%
S2/T1/V1	GTA	25	14	0.1690	0.1097	63%	75%
S2/T1/V4	GTC	26	14	0.0341	0.5483	60%	64%
S2/V-4/V-3	GCG	21	15	0.2632	0.2242	31%	41%
S2/V-4/V-3	GCA	10	4	0.2632	0.2265	6%	12%
S2/V-4/V-1	GCC	25	14	0.0366	0.0284	37%	52%
S2/V-4/V1	GCA	26	14	0.1022	0.0325	37%	52%
S2/V-4/V4	GCC	22	13	0.0745	0.4162	37%	44%
S2/V-3/V-1	GGC	23	14	0.0512	0.2187	31%	40%
S2/V-3/V1	GGA	23	14	0.1782	0.2350	31%	40%
S2/V-3/V4	GGC	23	14	0.0724	0.2110	31%	40%
S2/V-1/V1	GCA	21	11	0.0136	0.1562	65%	75%
S2/V-1/V4	GCC	23	12	0.0183	0.7501	62%	64%
S2/V1/V4	GAC	24	12	0.0220	0.8544	63%	64%
ST+4/ST+7/T1	AGT	22	18	0.3548	0.3529	28%	35%
ST+4/ST+7/T1	AAT	9	6	0.3548	0.5677	10%	14%

ST+4/ST+7/T1	CAT	7	3	0.3548	0.4114	6%	10%
ST+4/ST+7/V-4	AAC	10	6	0.3390	0.5491	9%	13%
ST+4/ST+7/V-4	CGC	8	5	0.3390	0.0996	4%	12%
ST+4/ST+7/V-4	CAG	5	2	0.3390	0.6496	2%	3%
ST+4/ST+7/V-3	AAG	10	5	0.5304	0.6584	9%	12%
ST+4/ST+7/V-3	CAA	5	2	0.5304	0.7353	4%	5%
ST+4/ST+7/V-1	AAA	9	5	0.7425	0.7309	11%	12%
ST+4/ST+7/V-1	CAC	6	3	0.7425	0.4572	4%	7%
ST+4/ST+7/V1	AAA	9	6	0.7332	0.4678	9%	14%
ST+4/ST+7/V1	CAA	7	3	0.7332	0.9093	4%	4%
ST+4/ST+7/V4	AAG	9	6	0.8049	0.9930	10%	10%
ST+4/ST+7/V4	CAC	7	3	0.8049	0.0393	2%	12%
ST+4/T1/V-4	ATC	27	17	0.1959	0.1428	39%	49%
ST+4/T1/V-3	ATG	29	17	0.1152	0.1478	39%	49%
ST+4/T1/V-1	ATC	26	18	0.2780	0.2841	28%	36%
ST+4/T1/V-1	ATA	9	5	0.2780	0.6305	11%	13%
ST+4/T1/V1	ATA	30	19	0.2046	0.2079	39%	49%
ST+4/T1/V4	ATC	26	18	0.3615	0.2058	29%	39%
ST+4/V-4/V-3	CCA	10	4	0.5034	0.2186	6%	12%
ST+4/V-4/V-1	ACA	9	5	0.5187	0.7087	10%	12%
ST+4/V-4/V-1	CCC	8	4	0.5187	0.1171	6%	15%
ST+4/V-4/V1	CCA	9	4	0.4787	0.1271	6%	13%
ST+4/V-4/V4	ACG	9	6	0.5365	0.9865	9%	9%
ST+4/V-3/V-1	AGA	8	5	0.8768	0.6518	9%	11%
ST+4/V-3/V1	AGA	18	16	0.9002	0.5190	63%	57%
ST+4/V-3/V4	AGG	9	5	0.8812	0.8224	10%	11%
ST+4/V-1/V1	AAA	9	5	0.7650	0.6960	9%	11%
ST+4/V-1/V4	AAG	9	5	0.8719	0.9612	10%	10%
ST+4/V1/V4	AAG	9	6	0.9477	0.8102	10%	11%
ST+7/T1/V-4	GTC	25	17	0.1692	0.0292	34%	49%
ST+7/T1/V-3	GTG	21	17	0.2897	0.2262	30%	38%
ST+7/T1/V-3	ATG	10	6	0.2897	0.3788	13%	19%
ST+7/T1/V-3	ATA	5	2	0.2897	0.6710	4%	5%
ST+7/T1/V-1	GTC	21	19	0.3173	0.2517	59%	68%
ST+7/T1/V-1	ATA	10	6	0.3173	0.5245	13%	17%
ST+7/T1/V-1	ATC	6	3	0.3173	0.4176	4%	7%
ST+7/T1/V1	GTA	20	18	0.2786	0.2771	59%	68%
ST+7/T1/V1	ATA	14	7	0.2786	0.4626	13%	18%
ST+7/T1/V4	ATG	10	7	0.4356	0.4475	15%	10%
ST+7/T1/V4	ATC	7	3	0.4356	0.0113	2%	14%
ST+7/V-4/V-3	ACG	12	6	0.2031	0.3145	13%	20%
ST+7/V-4/V-3	GCA	8	4	0.2031	0.1589	4%	10%
ST+7/V-4/V-3	AGA	5	2	0.2031	0.6900	2%	4%
ST+7/V-4/V-1	ACA	10	6	0.3713	0.5404	13%	17%
ST+7/V-4/V-1	AGC	5	2	0.3713	0.9339	4%	4%
ST+7/V-4/V1	ACA	9	5	0.4848	0.4806	10%	14%
ST+7/V-4/V1	AGA	5	2	0.4848	0.7963	3%	3%
ST+7/V-4/V4	ACG	10	7	0.5892	0.4067	15%	10%
ST+7/V-4/V4	AGC	5	2	0.5892	0.5651	2%	4%

ST+7/V-3/V-1	AGA	10	6	0.5478	0.5473	13%	17%
ST+7/V-3/V-1	AAC	5	2	0.5478	0.8828	4%	5%
ST+7/V-3/V1	AGA	9	5	0.7070	0.4781	9%	13%
ST+7/V-3/V1	AAA	5	2	0.7070	0.7782	4%	5%
ST+7/V-3/V4	AGG	10	6	0.5801	0.5298	13%	10%
ST+7/V-3/V4	AAC	5	2	0.5801	0.4667	2%	6%
ST+7/V-1/V1	AAA	9	5	0.4477	0.7662	9%	11%
ST+7/V-1/V1	ACA	6	3	0.4477	0.3813	4%	7%
ST+7/V-1/V4	AAG	10	6	0.4274	0.4914	13%	10%
ST+7/V-1/V4	ACC	6	3	0.4274	0.1608	2%	7%
ST+7/V1/V4	AAG	9	6	0.5587	0.8452	11%	10%
ST+7/V1/V4	AAC	7	3	0.5587	0.0940	2%	8%
T1/V-4/V-3	TCG	27	17	0.1625	0.0805	43%	57%
T1/V-4/V-1	TCC	28	17	0.1375	0.0195	35%	52%
T1/V-4/V1	TCA	30	15	0.0634	0.0118	44%	63%
T1/V-4/V4	TCC	25	16	0.1619	0.0221	31%	50%
T1/V-4/V4	TCG	15	10	0.1619	0.6969	17%	19%
T1/V-3/V-1	TGC	26	17	0.1887	0.1694	30%	40%
T1/V-3/V1	TGA	29	17	0.1190	0.1350	39%	51%
T1/V-3/V4	TGC	26	17	0.2506	0.0441	30%	46%
T1/V-1/V1	TCA	21	15	0.2331	0.1224	63%	75%
T1/V-1/V1	TAA	9	5	0.2331	0.6881	9%	11%
T1/V-1/V4	TCC	23	16	0.2886	0.6081	60%	64%
T1/V1/V4	TAC	24	16	0.2589	0.5190	60%	65%
V-4/V-3/V-1	CGA	10	7	0.5882	0.4925	13%	17%
V-4/V-3/V-1	CAC	8	4	0.5882	0.2001	6%	12%
V-4/V-3/V1	CGA	17	15	0.6246	0.6591	63%	59%
V-4/V-3/V1	CAA	8	4	0.6246	0.1913	6%	12%
V-4/V-3/V4	CGG	10	7	0.7396	0.5137	13%	10%
V-4/V-3/V4	CAG	7	4	0.7396	0.1026	3%	10%
V-4/V-1/V1	CCA	17	15	0.6155	0.8907	59%	60%
V-4/V-1/V1	CAA	9	5	0.6155	0.7730	9%	11%
V-4/V-1/V4	CAG	10	7	0.7073	0.5108	13%	10%
V-4/V-1/V4	CCG	7	4	0.7073	0.3859	4%	8%
V-4/V1/V4	CAG	14	8	0.6178	0.3492	13%	19%
V-3/V-1/V1	GAA	8	5	0.8524	0.7741	9%	11%
V-3/V-1/V4	GAG	10	7	0.9237	0.5208	13%	10%
V-3/V1/V4	GAG	9	5	0.8664	0.9426	10%	10%
V-1/V1/V4	AAG	9	5	0.7290	0.8938	9%	10%
S1/T1/V-1/V1	GTCA	21	14	0.1996	0.1265	63%	75%
S1/T1/V-1/V1	ATAA	9	5	0.1996	0.7387	9%	10%
S1/T1/V-1/V4	GTCC	23	15	0.2712	0.6250	60%	64%
S1/T1/V-1/V4	ATAG	9	5	0.2712	0.9606	10%	10%
S1/T1/V1/V4	GTAC	24	15	0.2788	0.5740	60%	65%
S1/T1/V1/V4	ATAG	9	6	0.2788	0.7658	8%	10%
S1/V-1/V1/V4	AAAG	9	5	0.7360	0.9308	9%	10%
S2/ST+7/T1/V-4	GGTC	23	14	0.0638	0.0391	35%	49%
S2/ST+7/T1/V-4	CATC	10	7	0.0638	0.5190	13%	17%
S2/ST+7/T1/V-4	GATG	5	1	0.0638	0.9031	4%	4%

S2/ST+7/T1/V-3	GGTG	19	14	0.0770	0.2353	30%	38%
S2/ST+7/T1/V-3	CATG	10	6	0.0770	0.5080	13%	17%
S2/ST+7/T1/V-3	GATA	5	1	0.0770	0.8427	4%	5%
S2/ST+7/T1/V-1	GGTC	24	18	0.0650	0.2358	59%	68%
S2/ST+7/T1/V-1	CATA	10	6	0.0650	0.4659	13%	17%
S2/ST+7/T1/V-1	GATC	6	2	0.0650	0.4282	4%	7%
S2/ST+7/T1/V4	GGTC	21	16	0.0855	0.7703	59%	57%
S2/ST+7/T1/V4	CATG	10	7	0.0855	0.5058	13%	10%
S2/ST+7/T1/V4	GATC	7	2	0.0855	0.1434	2%	7%
S2/ST+7/V-4/V-1	GGCC	23	14	0.0329	0.0722	37%	49%
S2/ST+7/V-4/V-1	CACA	10	6	0.0329	0.4878	13%	17%
S2/ST+7/V-4/V-1	GAGC	5	1	0.0329	0.9092	4%	4%
S2/ST+7/V-4/V4	GGCC	19	13	0.0852	0.9322	37%	38%
S2/ST+7/V-4/V4	CACG	10	7	0.0852	0.5055	13%	9%
S2/ST+7/V-4/V4	GAGC	5	1	0.0852	0.8599	2%	3%
S2/ST+7/V-3/V-1	GGGC	19	14	0.0622	0.3675	31%	38%
S2/ST+7/V-3/V-1	CAGA	10	6	0.0622	0.4791	13%	17%
S2/ST+7/V-3/V-1	GAAC	5	1	0.0622	0.8643	4%	5%
S2/ST+7/V-3/V4	GGGC	19	14	0.0897	0.5395	33%	38%
S2/ST+7/V-3/V4	CAGG	10	6	0.0897	0.5165	13%	10%
S2/ST+7/V-3/V4	GAAC	5	1	0.0897	0.5305	2%	5%
S2/ST+7/V-1/V4	GGCC	20	15	0.0659	0.5887	61%	57%
S2/ST+7/V-1/V4	CAAG	10	6	0.0659	0.5003	13%	10%
S2/ST+7/V-1/V4	GACC	6	2	0.0659	0.1538	2%	7%
S2/T1/V-4/V-1	GTCC	26	14	0.0468	0.0178	35%	52%
S2/T1/V-4/V4	GTCC	23	13	0.1053	0.1259	31%	44%
S2/T1/V-3/V-1	GTGC	24	14	0.0533	0.1595	30%	40%
S2/T1/V-3/V4	GTGC	24	14	0.0798	0.1451	30%	40%
S2/T1/V-1/V4	GTCC	25	14	0.0363	0.5912	60%	64%
S2/V-4/V-1/V4	GCCC	21	13	0.0637	0.1917	33%	44%
S2/V-4/V-1/V4	CCAG	10	6	0.0637	0.5145	13%	10%
S2/V-4/V-1/V4	GCCG	7	4	0.0637	0.3650	4%	9%
S2/V-3/V-1/V4	GGCC	23	14	0.0728	0.2225	31%	40%
S2/V-3/V-1/V4	CGAG	10	6	0.0728	0.5234	13%	10%
ST+7/T1/V-4/V-1	GTCC	26	17	0.1396	0.0388	35%	49%
ST+7/T1/V-4/V-1	ATCA	10	6	0.1396	0.4907	13%	17%
ST+7/T1/V-4/V-1	ATGC	5	2	0.1396	0.9054	4%	4%
ST+7/T1/V-4/V4	GTCC	22	16	0.3279	0.2892	33%	42%
ST+7/T1/V-4/V4	ATCG	10	7	0.3279	0.4104	15%	10%
ST+7/T1/V-4/V4	ATGC	5	2	0.3279	0.5611	2%	5%
ST+7/T1/V-3/V-1	GTGC	22	17	0.2605	0.2445	30%	38%
ST+7/T1/V-3/V-1	ATGA	10	6	0.2605	0.4780	13%	17%
ST+7/T1/V-3/V-1	ATAC	5	2	0.2605	0.8436	4%	5%
ST+7/T1/V-3/V4	GTGC	22	17	0.2859	0.3226	31%	39%
ST+7/T1/V-3/V4	ATGG	10	6	0.2859	0.5352	13%	10%
ST+7/T1/V-3/V4	ATAC	5	2	0.2859	0.4386	2%	6%
ST+7/T1/V-1/V4	ATAG	10	6	0.4356	0.5284	13%	10%
ST+7/T1/V-1/V4	ATCC	6	3	0.4356	0.1787	2%	7%
ST+7/V-4/V-1/V4	ACAG	10	6	0.4707	0.5224	13%	10%

ST+7/V-4/V-1/V4	GCCG	7	4	0.4707	0.3169	2%	7%
ST+7/V-4/V-1/V4	AGCC	5	2	0.4707	0.5401	2%	4%
ST+7/V-3/V-1/V4	AGAG	10	6	0.5730	0.5053	13%	10%
ST+7/V-3/V-1/V4	AACC	5	2	0.5730	0.4917	2%	5%
T1/V-4/V-1/V4	TCCC	24	16	0.2413	0.1299	31%	44%
T1/V-4/V-1/V4	TCAG	10	7	0.2413	0.5179	13%	10%
T1/V-4/V-1/V4	TCCG	7	4	0.2413	0.3666	4%	9%
T1/V-3/V-1/V4	TGCC	26	17	0.2414	0.1658	30%	40%
T1/V-3/V-1/V4	TGAG	10	7	0.2414	0.5361	13%	10%
T1/V-1/V1/V4	TCAC	23	16	0.2936	0.6233	60%	64%
T1/V-1/V1/V4	TAAG	9	5	0.2936	0.8825	9%	10%
S1/T1/V-1/V1/V4	GTCAC	23	15	0.2753	0.6149	60%	64%
S1/T1/V-1/V1/V4	ATAAG	9	5	0.2753	0.8705	9%	10%
S2/ST+7/T1/V-3/V-1	GGTGC	20	14	0.0675	0.2340	30%	38%
S2/ST+7/T1/V-3/V4	GGTGC	20	14	0.1049	0.3360	31%	38%
S2/ST+7/T1/V-1/V4	GGTCC	21	16	0.1071	0.7706	59%	57%
S2/ST+7/V-3/V-1/V4	GGGCC	19	14	0.0934	0.4946	33%	38%
S2/T1/V-3/V-1/V4	GTGCC	24	14	0.0832	0.1609	30%	40%
ST+7/T1/V-3/V-1/V4	GTGCC	22	17	0.2899	0.3417	31%	38%

**TABLE 29**

BHR Combined							
SNP(s)	Over-Transmitted Allele or Haplo	T	NT	p-value	Case/Cntl	Case freq	Cntl freq
L-1	G	23	13	0.1325	0.8722	90%	89%
S1	G	22	11	0.0801	0.2251	94%	89%
S2	G	49	23	<b>0.0029</b>	0.2009	80%	74%
ST+4	A	52	50	0.9212	0.1521	59%	51%
ST+7	G	32	21	0.1690	0.3199	83%	78%
T1	T	27	13	0.0385	0.8750	88%	89%
V-4	G	43	40	0.8264	0.5602	27%	24%
V-3	A	48	46	0.9179	0.6016	40%	37%
V-1	C	27	16	0.1263	0.1413	91%	85%
V1	A	4	4	1.0000	0.7758	98%	96%
V4	C	43	28	0.0959	0.4009	80%	77%
L-1/S1	GG	38	18	0.0143	0.1048	85%	78%
L-1/S2	GG	48	21	0.0014	0.2486	79%	74%
L-1/ST+4	GA	53	41	0.1541	0.2543	48%	42%
L-1/ST+7	GG	50	26	0.0134	0.2022	73%	67%
L-1/T1	GT	25	13	0.0319	0.6689	87%	89%
L-1/V-4	GC	56	43	0.1621	0.6756	63%	65%
L-1/V-3	GG	52	40	0.1632	0.7599	50%	52%
L-1/V-1	GC	44	21	0.0077	0.0816	82%	74%
L-1/V1	GA	26	15	0.1266	0.5742	87%	85%
L-1/V4	GC	47	23	0.0086	0.4292	70%	66%

S1/S2	GG	48	22	0.0034	0.1752	80%	74%
S1/ST+4	GA	57	48	0.3771	0.0447	52%	42%
S1/ST+7	GG	34	23	0.1700	0.3759	82%	78%
S1/T1	GT	47	18	0.0005	0.1994	84%	78%
S1/V-4	GC	52	41	0.1848	0.7544	67%	65%
S1/V-3	GG	57	44	0.1529	0.7979	54%	53%
S1/V-1	GC	26	15	0.1079	0.1278	91%	85%
S1/V1	GA	25	15	0.1638	0.1181	91%	86%
S1/V4	GC	42	28	0.1187	0.2820	80%	76%
S2/ST+4	GA	64	34	0.0013	0.0315	42%	31%
S2/ST+7	GG	59	27	0.0008	0.3188	71%	67%
S2/T1	GT	52	21	0.0007	0.3241	78%	73%
S2/V-4	GC	69	37	0.0012	0.5749	53%	50%
S2/V-3	GG	62	31	0.0006	0.4098	41%	37%
S2/V-1	GC	50	22	0.0013	0.1822	80%	74%
S2/V1	GA	48	22	0.0011	0.1882	80%	74%
S2/V4	GC	52	25	0.0026	0.1222	70%	62%
ST+4/ST+7	AG	59	47	0.3780	0.0246	53%	40%
ST+4/T1	AT	59	38	0.0349	0.3575	47%	42%
ST+4/V-4	AC	52	47	0.9025	0.1754	59%	52%
ST+4/V-3	AG	54	45	0.2694	0.2016	59%	52%
ST+4/V-1	AC	60	47	0.3926	0.0251	53%	41%
ST+4/V1	AA	51	48	0.8934	0.1803	59%	52%
ST+4/V4	AC	57	48	0.5069	0.0554	52%	41%
ST+4/V4	CC	48	44	0.5069	0.1680	29%	36%
ST+7/T1	GT	56	26	0.0015	0.3638	71%	67%
ST+7/V-4	GC	59	43	0.1085	0.4137	63%	59%
ST+7/V-3	GG	62	44	0.2069	0.2855	52%	47%
ST+7/V-1	GC	37	26	0.2547	0.3697	82%	78%
ST+7/V1	GA	34	25	0.4463	0.2856	83%	78%
ST+7/V4	GC	44	31	0.1589	0.1891	72%	66%
T1/V-4	TC	58	41	0.0463	0.5267	61%	64%
T1/V-3	TG	58	37	0.0298	0.6184	49%	52%
T1/V-1	TC	54	25	0.0015	0.1493	80%	74%
T1/V1	TA	32	16	0.0270	0.8101	86%	85%
T1/V4	TC	58	25	0.0005	0.5730	69%	66%
V-4/V-3	CG	51	49	0.7270	0.6436	61%	63%
V-4/V-1	CC	55	41	0.1050	0.6063	64%	61%
V-4/V1	CA	41	40	1.0000	0.7749	71%	72%
V-4/V4	CC	56	43	0.3262	0.9335	53%	53%
V-3/V-1	GC	59	44	0.1696	0.6446	51%	48%
V-3/V1	GA	49	42	0.6640	0.7855	58%	59%
V-3/V4	GC	58	42	0.1799	0.9090	50%	51%
V-1/V1	CA	26	18	0.3190	0.1313	91%	85%
V-1/V4	CC	43	29	0.1529	0.0596	80%	73%
V1/V4	AC	43	28	0.1850	0.1074	80%	74%
L-1/S1/S2	GGG	42	21	0.0177	0.2379	79%	74%
L-1/S1/ST+4	GGA	51	30	0.0488	0.0296	43%	32%
L-1/S1/ST+7	GGG	45	26	0.0555	0.1976	73%	67%



L-1/S1/T1	GGT	40	17	0.0023	0.2745	83%	78%
L-1/S1/V-4	GGC	57	36	0.0563	0.4793	58%	54%
L-1/S1/V-3	GGG	51	31	0.0504	0.4982	45%	42%
L-1/S1/V-1	GGC	42	21	0.0247	0.0788	82%	74%
L-1/S1/V1	GGA	40	21	0.0376	0.0682	83%	75%
L-1/S1/V4	GGC	46	23	0.0164	0.2322	72%	66%
L-1/S2/ST+4	GGA	54	28	0.0067	0.0362	41%	31%
L-1/S2/ST+7	GGG	53	26	0.0075	0.4921	70%	67%
L-1/S2/T1	GGT	46	19	0.0008	0.4181	77%	74%
L-1/S2/V-4	GGC	61	34	0.0098	0.6998	52%	50%
L-1/S2/V-3	GGG	53	29	0.0058	0.4968	41%	37%
L-1/S2/V-1	GGC	44	21	0.0081	0.2466	79%	74%
L-1/S2/V1	GGA	43	21	0.0127	0.2512	79%	74%
L-1/S2/V4	GGC	45	23	0.0206	0.1223	70%	62%
L-1/ST+4/ST+7	GAG	55	31	0.0236	0.0135	44%	31%
L-1/ST+4/T1	GAT	50	34	0.0736	0.4328	46%	42%
L-1/ST+4/V-4	GAC	53	37	0.1398	0.2380	48%	42%
L-1/ST+4/V-3	GAG	51	35	0.0697	0.2416	48%	42%
L-1/ST+4/V-1	GAC	53	30	0.0407	0.0137	44%	31%
L-1/ST+4/V1	GAA	51	36	0.2038	0.2703	48%	42%
L-1/ST+4/V4	GAC	52	30	0.0534	0.0938	41%	32%
L-1/ST+7/T1	GGT	49	23	0.0025	0.4040	71%	67%
L-1/ST+7/V-4	GGC	62	36	0.0229	0.2573	54%	48%
L-1/ST+7/V-3	GGG	57	29	0.0145	0.1274	44%	36%
L-1/ST+7/V-1	GGC	48	26	0.0273	0.2345	73%	67%
L-1/ST+7/V1	GGA	45	25	0.0459	0.1613	74%	67%
L-1/ST+7/V4	GGC	47	24	0.0228	0.1637	63%	56%
L-1/T1/V-4	GTC	53	39	0.0340	0.4267	60%	64%
L-1/T1/V-3	GTG	49	34	0.0339	0.5133	48%	52%
L-1/T1/V-1	GTC	46	19	0.0007	0.2084	80%	74%
L-1/T1/V1	GTA	27	14	0.0695	0.9638	85%	85%
L-1/T1/V4	GTC	49	22	0.0019	0.7563	68%	66%
L-1/V-4/V-3	GCG	53	39	0.2250	0.7525	50%	52%
L-1/V-4/V-1	GCC	60	36	0.0260	0.4210	54%	50%
L-1/V-4/V1	GCA	53	40	0.2875	0.8650	60%	61%
L-1/V-4/V4	GCC	53	28	0.0308	0.9683	43%	43%
L-1/V-3/V-1	GGC	53	30	0.0170	0.5160	41%	37%
L-1/V-3/V1	GGA	49	35	0.2443	0.9138	48%	48%
L-1/V-3/V4	GGC	53	29	0.0356	0.7515	39%	41%
L-1/V-1/V1	GCA	42	21	0.0190	0.0699	82%	74%
L-1/V-1/V4	GCC	48	24	0.0126	0.0587	71%	62%
L-1/V1/V4	GAC	48	24	0.0195	0.1439	70%	63%
S1/S2/ST+4	GGA	58	32	0.0190	0.0553	41%	31%
S1/S2/ST+7	GGG	53	25	0.0037	0.4073	71%	67%
S1/S2/T1	GGT	50	21	0.0014	0.2995	78%	73%
S1/S2/V-4	GGC	64	36	0.0090	0.5949	53%	50%
S1/S2/V-3	GGG	57	30	0.0070	0.4288	41%	37%
S1/S2/V-1	GGC	48	22	0.0028	0.1741	80%	74%
S1/S2/V1	GGA	46	22	0.0060	0.1789	80%	74%

S1/S2/V4	GGC	51	25	0.0041	0.1649	69%	62%
S1/ST+4/ST+7	GAG	53	45	0.5356	0.0414	52%	41%
S1/ST+4/T1	GAT	61	33	0.0038	0.0665	41%	32%
S1/ST+4/V-4	GAC	55	42	0.4989	0.0384	53%	42%
S1/ST+4/V-3	GAG	55	40	0.3547	0.0458	52%	42%
S1/ST+4/V-1	GAC	57	47	0.4755	0.0425	52%	41%
S1/ST+4/V1	GAA	56	48	0.5976	0.0468	53%	42%
S1/ST+4/V4	GAC	55	48	0.2408	0.0395	52%	41%
S1/ST+4/V4	GCC	48	43	0.2408	0.1834	28%	35%
S1/ST+7/T1	GGT	54	24	0.0014	0.3068	72%	67%
S1/ST+7/V-4	GGC	53	41	0.3296	0.4823	63%	59%
S1/ST+7/V-3	GGG	55	41	0.3296	0.3876	52%	47%
S1/ST+7/V-1	GGC	34	23	0.2560	0.3700	82%	78%
S1/ST+7/V1	GGA	32	23	0.3742	0.3676	82%	78%
S1/ST+7/V4	GGC	42	31	0.4131	0.2343	72%	66%
S1/T1/V-4	GTC	67	37	0.0025	0.6275	56%	54%
S1/T1/V-3	GTG	62	31	0.0010	0.6604	43%	41%
S1/T1/V-1	GTC	51	21	0.0006	0.1410	81%	74%
S1/T1/V1	GTA	49	21	0.0016	0.1381	81%	75%
S1/T1/V4	GTC	57	25	0.0006	0.3622	70%	66%
S1/V-4/V-3	GCG	55	43	0.2440	0.7158	55%	53%
S1/V-4/V-1	GCC	53	41	0.2603	0.5991	64%	61%
S1/V-4/V1	GCA	52	41	0.3277	0.5858	64%	62%
S1/V-4/V4	GCC	55	43	0.3616	0.9319	53%	53%
S1/V-3/V-1	GGC	57	43	0.2097	0.6435	51%	48%
S1/V-3/V1	GGA	56	42	0.2543	0.6446	52%	49%
S1/V-3/V4	GGC	57	42	0.2593	0.9744	51%	51%
S1/V-1/V1	GCA	24	15	0.1750	0.1243	91%	85%
S1/V-1/V4	GCC	42	29	0.3043	0.0622	80%	73%
S1/V1/V4	GAC	42	28	0.2798	0.0804	80%	73%
S2/ST+4/ST+7	GAG	59	31	0.0122	0.0440	42%	32%
S2/ST+4/T1	GAT	61	30	0.0024	0.0560	41%	31%
S2/ST+4/V-4	GAC	61	29	0.0029	0.0326	42%	31%
S2/ST+4/V-3	GAG	60	27	0.0013	0.0299	42%	31%
S2/ST+4/V-1	GAC	60	30	0.0052	0.0260	42%	31%
S2/ST+4/V1	GAA	59	32	0.0059	0.0456	42%	32%
S2/ST+4/V4	GAC	58	31	0.0096	0.0284	42%	31%
S2/ST+7/T1	GGT	58	23	0.0005	0.5726	69%	67%
S2/ST+7/V-4	GGC	67	37	0.0074	0.3517	52%	48%
S2/ST+7/V-3	GGG	60	29	0.0017	0.2361	41%	35%
S2/ST+7/V-1	GGC	56	25	0.0011	0.3811	71%	67%
S2/ST+7/V1	GGA	54	25	0.0028	0.3093	71%	67%
S2/ST+7/V4	GGC	53	23	0.0014	0.2431	61%	55%
S2/T1/V-4	GTC	68	33	0.0007	0.7752	51%	50%
S2/T1/V-3	GTG	61	27	0.0004	0.5910	40%	37%
S2/T1/V-1	GTC	52	21	0.0008	0.2977	78%	74%
S2/T1/V1	GTA	50	21	0.0014	0.3135	78%	73%
S2/T1/V4	GTC	54	24	0.0014	0.1684	69%	62%
S2/V-4/V-3	GCG	61	30	0.0013	0.3609	42%	37%

S2/V-4/V-1	GCC	66	36	0.0057	0.5756	53%	50%
S2/V-4/V1	GCA	64	36	0.0061	0.5814	53%	50%
S2/V-4/V4	GCC	58	30	0.0085	0.4929	43%	39%
S2/V-3/V-1	GGC	59	30	0.0039	0.4388	41%	37%
S2/V-3/V1	GGA	58	30	0.0019	0.4186	41%	37%
S2/V-3/V4	GGC	58	29	0.0095	0.4119	41%	37%
S2/V-1/V1	GCA	48	22	0.0028	0.1870	80%	74%
S2/V-1/V4	GCC	52	25	0.0044	0.1180	70%	62%
S2/V1/V4	GAC	51	25	0.0070	0.1295	70%	62%
ST+4/ST+7/T1	AGT	59	31	0.0056	0.0249	42%	31%
ST+4/ST+7/V-4	AGC	57	43	0.4266	0.0214	53%	40%
ST+4/ST+7/V-3	AGG	58	41	0.1257	0.0279	52%	41%
ST+4/ST+7/V-1	AGC	55	45	0.5850	0.0459	52%	41%
ST+4/ST+7/V1	AGA	54	44	0.7186	0.0225	53%	41%
ST+4/ST+7/V4	AGC	54	44	0.4963	0.0445	52%	41%
ST+4/T1/V-4	ATC	57	35	0.0482	0.3350	47%	42%
ST+4/T1/V-3	ATG	57	31	0.0122	0.3205	47%	42%
ST+4/T1/V-1	ATC	64	32	0.0035	0.0382	42%	31%
ST+4/T1/V1	ATA	58	39	0.0709	0.3881	47%	42%
ST+4/T1/V4	ATC	61	33	0.0091	0.1890	39%	32%
ST+4/V-4/V-3	ACG	52	43	0.5684	0.1911	59%	52%
ST+4/V-4/V-1	ACC	58	42	0.3077	0.0257	53%	41%
ST+4/V-4/V1	ACA	48	42	0.9287	0.1811	59%	52%
ST+4/V-4/V4	ACC	56	41	0.5494	0.0568	51%	41%
ST+4/V-3/V-1	AGC	57	40	0.3334	0.0511	52%	42%
ST+4/V-3/V1	AGA	50	39	0.2924	0.2092	59%	52%
ST+4/V-3/V4	AGC	57	40	0.4375	0.0693	51%	40%
ST+4/V-1/V1	ACA	58	46	0.5063	0.0525	52%	42%
ST+4/V-1/V4	ACC	57	46	0.4471	0.0276	52%	41%
ST+4/V1/V4	AAC	56	47	0.6497	0.0672	51%	41%
ST+4/V1/V4	CAC	47	43	0.6497	0.4518	29%	33%
ST+7/T1/V-4	GTC	69	35	0.0005	0.3805	52%	48%
ST+7/T1/V-3	GTG	62	29	0.0014	0.2233	42%	36%
ST+7/T1/V-1	GTC	57	27	0.0017	0.3649	71%	67%
ST+7/T1/V1	GTA	53	26	0.0064	0.3048	72%	67%
ST+7/T1/V4	GTC	55	23	0.0003	0.2847	61%	56%
ST+7/V-4/V-3	GCG	60	42	0.0962	0.3945	52%	47%
ST+7/V-4/V-1	GCC	56	41	0.1140	0.3907	63%	59%
ST+7/V-4/V1	GCA	55	41	0.1867	0.3728	63%	59%
ST+7/V-4/V4	GCC	54	42	0.3231	0.2923	53%	47%
ST+7/V-3/V-1	GGC	58	42	0.1838	0.4211	51%	47%
ST+7/V-3/V1	GGA	57	41	0.3772	0.3322	52%	47%
ST+7/V-3/V4	GGC	57	41	0.2255	0.4291	51%	47%
ST+7/V-1/V1	GCA	35	26	0.4851	0.3705	82%	78%
ST+7/V-1/V4	GCC	44	31	0.2351	0.1928	72%	66%
ST+7/V1/V4	GAC	43	30	0.3692	0.2092	72%	66%
T1/V-4/V-3	TCG	55	38	0.0606	0.6211	49%	52%
T1/V-4/V-1	TCC	71	36	0.0011	0.5931	52%	50%
T1/V-4/V1	TCA	58	40	0.0651	0.7094	59%	61%

T1/V-4/V4	TCC	62	30	0.0017	0.8367	42%	43%
T1/V-3/V-1	TGC	64	30	0.0005	0.6315	39%	37%
T1/V-3/V1	TGA	57	34	0.0359	0.7628	47%	48%
T1/V-3/V4	TGC	63	29	0.0008	0.6108	38%	41%
T1/V-1/V1	TCA	50	24	0.0052	0.1370	81%	74%
T1/V-1/V4	TCC	58	25	0.0004	0.1180	70%	62%
T1/V1/V4	TAC	58	25	0.0009	0.2415	69%	63%
V-4/V-3/V-1	CGC	57	42	0.1009	0.5392	52%	48%
V-4/V-3/V1	CGA	47	42	0.7212	0.8728	59%	60%
V-4/V-3/V4	CGC	56	41	0.2915	0.9801	51%	52%
V-4/V-1/V1	CCA	54	41	0.2066	0.5975	64%	61%
V-4/V-1/V4	CCC	56	43	0.2922	0.4415	53%	49%
V-4/V1/V4	CAC	55	42	0.5831	0.5278	53%	50%
V-3/V-1/V1	GCA	58	43	0.2585	0.6480	51%	48%
V-3/V-1/V4	GCC	58	42	0.2775	0.5942	51%	48%
V-3/V1/V4	GAC	57	41	0.4090	0.7209	50%	48%
V-1/V1/V4	CAC	42	28	0.2281	0.0639	80%	73%
S1/T1/V-1/V1	GTCA	48	21	0.0020	0.1388	81%	74%
S1/T1/V-1/V4	GTCC	57	25	0.0011	0.1077	70%	62%
S1/T1/V1/V4	GTAC	57	25	0.0021	0.1265	70%	63%
S1/V-1/V1/V4	GCAC	41	28	0.3483	0.0637	80%	73%
S2/ST+7/T1/V-4	GGTC	67	33	0.0006	0.4249	51%	47%
S2/ST+7/T1/V-3	GGTG	59	26	0.0006	0.4483	40%	36%
S2/ST+7/T1/V-1	GGTC	58	23	0.0005	0.5809	69%	67%
S2/ST+7/T1/V4	GGTC	55	21	0.0004	0.3101	60%	55%
S2/ST+7/V-4/V-1	GGCC	65	36	0.0095	0.3696	52%	48%
S2/ST+7/V-4/V4	GGCC	55	29	0.0230	0.1658	44%	36%
S2/ST+7/V-3/V-1	GGGC	57	28	0.0048	0.2744	41%	36%
S2/ST+7/V-3/V4	GGGC	56	28	0.0124	0.2638	41%	36%
S2/ST+7/V-1/V4	GGCC	53	23	0.0015	0.2522	61%	55%
S2/T1/V-4/V-1	GTCC	68	33	0.0005	0.6143	52%	49%
S2/T1/V-4/V4	GTCC	60	27	0.0024	0.6594	42%	39%
S2/T1/V-3/V-1	GTGC	61	27	0.0005	0.6850	39%	37%
S2/T1/V-3/V4	GTGC	60	26	0.0019	0.6076	40%	37%
S2/T1/V-1/V4	GTCC	54	24	0.0029	0.1663	69%	62%
S2/V-4/V-1/V4	GCCC	58	30	0.0132	0.3435	44%	39%
S2/V-3/V-1/V4	GGCC	58	29	0.0140	0.4526	41%	37%
ST+7/T1/V-4/V-1	GTCC	69	35	0.0010	0.4073	52%	48%
ST+7/T1/V-4/V4	GTCC	59	28	0.0008	0.4429	41%	37%
ST+7/T1/V-3/V-1	GTGC	62	29	0.0013	0.4143	40%	36%
ST+7/T1/V-3/V4	GTGC	61	28	0.0009	0.4750	40%	36%
ST+7/T1/V-1/V4	GTCC	55	23	0.0005	0.2653	61%	55%
ST+7/V-4/V-1/V4	GCCC	54	42	0.3202	0.2691	53%	47%
ST+7/V-3/V-1/V4	GGCC	57	41	0.2098	0.4099	51%	47%
T1/V-4/V-1/V4	TCCC	62	29	0.0005	0.5872	42%	39%
T1/V-3/V-1/V4	TGCC	63	28	0.0010	0.6404	40%	37%
T1/V-1/V1/V4	TCAAC	57	25	0.0005	0.1026	70%	62%
S1/T1/V-1/V1/V4	GTCAC	56	25	0.0020	0.1001	70%	62%
S2/ST+7/T1/V-3/V-1	GGTGC	59	26	0.00013	0.4598	40%	36%

S2/ST+7/T1/V-3/V4	GGTGC	58	26	0.0030	0.4615	40%	36%
S2/ST+7/T1/V-1/V4	GGTCC	55	21	0.00013	0.3216	60%	55%
S2/ST+7/V-3/V-1/V4	GGGCC	56	28	0.0103	0.2865	41%	36%
S2/T1/V-3/V-1/V4	GTGCC	60	26	0.0030	0.6814	40%	37%
ST+7/T1/V-3/V-1/V4	GTGCC	61	28	0.00024	0.4308	40%	36%

**TABLE 29 (CON'T)**

BHR UK							
SNP(s)	Over-Transmitted Allele or Haplo	T	NT	TDT p-value	Case/Cntl p-value	Case freq	Cntl freq
L-1	G	13	11	0.8388	0.0899	94%	87%
S1	G	19	5	0.0066	0.0603	96%	89%
S2	G	37	16	0.0055	0.0038	87%	73%
ST+4	A	43	39	0.7407	0.1538	57%	48%
ST+7	G	29	13	0.0195	0.2294	86%	80%
T1	T	16	10	0.3269	0.1041	93%	87%
V-4	C	34	34	1.0000	0.7889	73%	75%
V-3	G	38	36	0.9076	0.5461	58%	62%
V-1	C	23	9	0.0201	0.0454	94%	86%
V1	A	3	3	1.0000	1.0000	98%	98%
V4	C	38	21	0.0363	0.2122	82%	75%
L-1/S1	GG	28	12	0.0116	0.0036	91%	77%
L-1/S2	GG	37	14	0.0007	0.0071	86%	73%
L-1/ST+4	GA	40	34	0.6901	0.0475	51%	38%
L-1/ST+7	GG	40	17	0.0023	0.0111	81%	67%
L-1/T1	GT	15	10	0.1504	0.2233	92%	87%
L-1/V-4	GC	42	35	0.6696	0.4106	67%	62%
L-1/V-3	GG	39	32	0.6574	0.6144	52%	49%
L-1/V-1	GC	33	14	0.0054	0.0018	89%	74%
L-1/V1	GA	16	12	0.6763	0.1050	92%	85%
L-1/V4	GC	36	18	0.0327	0.0266	76%	63%
S1/S2	GG	37	15	0.0020	0.0042	87%	73%
S1/ST+4	GA	49	36	0.0778	0.0171	53%	39%
S1/ST+7	GG	30	13	0.0076	0.3019	85%	80%
S1/T1	GT	35	11	0.00015	0.0057	90%	76%
S1/V-4	GC	43	27	0.0188	0.3569	69%	64%
S1/V-3	GG	49	31	0.0251	0.6440	54%	51%
S1/V-1	GC	22	8	0.0091	0.0359	94%	86%
S1/V1	GA	21	8	0.0133	0.0746	94%	87%
S1/V4	GC	37	21	0.0168	0.1158	82%	75%
S2/ST+4	GA	54	28	0.0035	0.0017	48%	28%
S2/ST+7	GG	47	17	0.00013	0.0250	78%	66%
S2/T1	GT	40	13	0.00017	0.0097	86%	72%
S2/V-4	GC	56	28	0.0023	0.0488	60%	49%
S2/V-3	GG	53	25	0.0015	0.0452	47%	36%

S2/V-1	GC	39	15	0.0014	0.0035	87%	73%
S2/V1	GA	37	15	0.0020	0.0062	87%	73%
S2/V4	GC	42	20	0.0025	0.0106	75%	61%
ST+4/ST+7	AG	51	34	0.0533	0.0118	55%	39%
ST+4/T1	AT	45	31	0.1929	0.0545	50%	38%
ST+4/V-4	AC	44	35	0.6758	0.1419	58%	48%
ST+4/V-3	AG	47	33	0.1039	0.1704	57%	48%
ST+4/V-1	AC	52	35	0.0916	0.0076	55%	39%
ST+4/V1	AA	42	38	0.8061	0.1664	57%	48%
ST+4/V4	AC	49	36	0.1756	0.0199	53%	37%
ST+7/T1	GT	45	17	0.0003	0.0146	80%	66%
ST+7/V-4	GC	51	29	0.0054	0.2473	67%	61%
ST+7/V-3	GG	55	31	0.0170	0.2386	55%	48%
ST+7/V-1	GC	33	16	0.0223	0.2882	85%	80%
ST+7/V1	GA	31	16	0.0321	0.1785	86%	80%
ST+7/V4	GC	41	23	0.0086	0.3028	72%	67%
T1/V-4	TC	43	33	0.3496	0.4354	66%	62%
T1/V-3	TG	44	29	0.1472	0.6521	52%	49%
T1/V-1	TC	41	17	0.0020	0.0039	88%	73%
T1/V1	TA	20	12	0.2895	0.1189	91%	85%
T1/V4	TC	46	19	0.0018	0.0369	75%	63%
V-4/V-3	CG	42	37	0.5926	0.5775	59%	62%
V-4/V-1	CC	47	28	0.0095	0.2929	67%	61%
V-4/V1	CA	35	32	0.8785	0.7463	71%	73%
V-4/V4	CC	49	31	0.0742	0.4011	55%	50%
V-3/V-1	GC	52	32	0.0350	0.5466	52%	49%
V-3/V1	GA	42	32	0.4122	0.5624	56%	60%
V-3/V4	GC	51	30	0.0143	0.6351	52%	49%
V-1/V1	CA	22	11	0.0559	0.0445	94%	86%
V-1/V4	CC	38	22	0.0218	0.0545	82%	73%
V1/V4	AC	38	21	0.0535	0.0919	82%	74%
L-1/S1/S2	GGG	32	14	0.0117	0.0091	86%	73%
L-1/S1/ST+4	GGA	41	23	0.0429	0.0006	51%	29%
L-1/S1/ST+7	GGG	34	16	0.0189	0.0138	80%	67%
L-1/S1/T1	GGT	29	10	0.0007	0.0104	89%	76%
L-1/S1/V-4	GGC	45	25	0.0203	0.0434	64%	52%
L-1/S1/V-3	GGG	41	23	0.0367	0.0258	52%	39%
L-1/S1/V-1	GGC	31	14	0.0178	0.0027	89%	74%
L-1/S1/V1	GGA	29	14	0.0343	0.0044	89%	75%
L-1/S1/V4	GGC	35	18	0.0238	0.0198	77%	64%
L-1/S2/ST+4	GGA	45	22	0.0075	0.0013	48%	28%
L-1/S2/ST+7	GGG	42	16	0.0013	0.0382	77%	66%
L-1/S2/T1	GGT	35	11	0.00003	0.0146	85%	73%
L-1/S2/V-4	GGC	50	25	0.0063	0.0794	59%	48%
L-1/S2/V-3	GGG	45	23	0.0080	0.0514	47%	35%
L-1/S2/V-1	GGC	34	14	0.0048	0.0076	86%	73%
L-1/S2/V1	GGA	33	14	0.0084	0.0096	86%	73%
L-1/S2/V4	GGC	35	18	0.0102	0.0128	75%	61%
L-1/ST+4/ST+7	GAG	45	24	0.0174	0.0009	50%	29%

L-1/ST+4/T1	GAT	37	27	0.1818	0.0740	49%	38%
L-1/ST+4/V-4	GAC	41	30	0.4742	0.0370	51%	38%
L-1/ST+4/V-3	GAG	40	28	0.2165	0.0376	51%	38%
L-1/ST+4/V-1	GAC	43	23	0.0305	0.0002	51%	28%
L-1/ST+4/V1	GAA	38	29	0.6152	0.0521	51%	38%
L-1/ST+4/V4	GAC	42	23	0.0519	0.0021	47%	28%
L-1/ST+7/T1	GGT	39	14	0.00007	0.0232	79%	67%
L-1/ST+7/V-4	GGC	51	26	0.0055	0.0222	62%	48%
L-1/ST+7/V-3	GGG	48	22	0.0044	0.0125	50%	35%
L-1/ST+7/V-1	GGC	37	16	0.0060	0.0160	80%	67%
L-1/ST+7/V1	GGA	35	16	0.0133	0.0063	81%	67%
L-1/ST+7/V4	GGC	38	18	0.0102	0.0538	67%	55%
L-1/T1/V-4	GTC	40	31	0.1656	0.5227	65%	62%
L-1/T1/V-3	GTG	36	26	0.1445	0.7708	51%	49%
L-1/T1/V-1	GTC	34	11	0.00012	0.0069	87%	73%
L-1/T1/V1	GTA	16	10	0.2576	0.2318	90%	85%
L-1/T1/V4	GTC	37	16	0.0044	0.0644	74%	64%
L-1/V-4/V-3	GCG	39	31	0.7040	0.8053	53%	49%
L-1/V-4/V-1	GCC	49	26	0.0083	0.0358	62%	49%
L-1/V-4/V1	GCA	42	33	0.6803	0.4450	65%	60%
L-1/V-4/V4	GCC	44	21	0.0304	0.1033	49%	39%
L-1/V-3/V-1	GGC	44	23	0.0160	0.0725	47%	36%
L-1/V-3/V1	GGA	38	28	0.5633	0.6053	50%	47%
L-1/V-3/V4	GGC	44	22	0.0189	0.1902	46%	38%
L-1/V-1/V1	GCA	31	14	0.0130	0.0018	89%	74%
L-1/V-1/V4	GCC	37	19	0.0126	0.0065	76%	62%
L-1/V1/V4	GAC	37	19	0.0577	0.0105	76%	62%
S1/S2/ST+4	GGA	48	26	0.0224	0.0038	47%	29%
S1/S2/ST+7	GGG	41	15	0.0007	0.0274	78%	66%
S1/S2/T1	GGT	38	13	0.0004	0.0085	86%	72%
S1/S2/V-4	GGC	52	27	0.0057	0.0647	60%	49%
S1/S2/V-3	GGG	48	24	0.0092	0.0618	47%	36%
S1/S2/V-1	GGC	37	15	0.0034	0.0046	87%	73%
S1/S2/V1	GGA	35	15	0.0054	0.0043	87%	73%
S1/S2/V4	GGC	41	20	0.0084	0.0185	75%	61%
S1/ST+4/ST+7	GAG	45	33	0.0935	0.0181	53%	39%
S1/ST+4/T1	GAT	50	26	0.0028	0.0003	50%	28%
S1/ST+4/V-4	GAC	48	30	0.0638	0.0063	55%	39%
S1/ST+4/V-3	GAG	48	28	0.0600	0.0203	53%	39%
S1/ST+4/V-1	GAC	49	35	0.0896	0.0160	53%	38%
S1/ST+4/V1	GAA	48	36	0.1558	0.0211	53%	39%
S1/ST+4/V4	GAC	47	36	0.0625	0.0110	53%	38%
S1/ST+7/T1	GGT	42	14	0.00012	0.0253	79%	66%
S1/ST+7/V-4	GGC	45	28	0.0361	0.3136	67%	61%
S1/ST+7/V-3	GGG	48	29	0.0295	0.4047	53%	48%
S1/ST+7/V-1	GGC	30	13	0.0117	0.2931	85%	80%
S1/ST+7/V1	GGA	28	13	0.0260	0.2911	85%	80%
S1/ST+7/V4	GGC	39	23	0.0325	0.4346	71%	67%
S1/T1/V-4	GTC	52	26	0.0013	0.0448	63%	51%

S1/T1/V-3	GTG	50	23	0.0008	0.0282	52%	38%
S1/T1/V-1	GTC	38	13	0.00018	0.0029	88%	73%
S1/T1/V1	GTA	36	13	0.0008	0.0059	88%	74%
S1/T1/V4	GTC	45	19	0.0006	0.0286	76%	63%
S1/V-4/V-3	GCG	47	30	0.0277	0.4330	56%	51%
S1/V-4/V-1	GCC	45	28	0.0212	0.4023	67%	62%
S1/V-4/V1	GCA	44	28	0.0361	0.4281	67%	63%
S1/V-4/V4	GCC	48	31	0.0423	0.3538	55%	50%
S1/V-3/V-1	GGC	50	31	0.0259	0.5545	52%	49%
S1/V-3/V1	GGA	49	30	0.0326	0.6543	52%	49%
S1/V-3/V4	GGC	50	30	0.0138	0.6664	53%	50%
S1/V-1/V1	GCA	20	8	0.0191	0.0341	94%	86%
S1/V-1/V4	GCC	37	22	0.0454	0.0589	82%	73%
S1/V1/V4	GAC	37	21	0.0427	0.0773	82%	73%
S2/ST+4/ST+7	GAG	49	25	0.0102	0.0024	48%	29%
S2/ST+4/T1	GAT	51	24	0.0027	0.0011	48%	28%
S2/ST+4/V-4	GAC	52	23	0.0069	0.0013	49%	28%
S2/ST+4/V-3	GAG	51	21	0.0038	0.0005	48%	28%
S2/ST+4/V-1	GAC	50	24	0.0096	0.0012	49%	28%
S2/ST+4/V1	GAA	49	26	0.0126	0.0009	48%	29%
S2/ST+4/V4	GAC	48	25	0.0135	0.0019	47%	28%
S2/ST+7/T1	GGT	46	13	0.000022	0.0419	77%	66%
S2/ST+7/V-4	GGC	55	28	0.0036	0.0358	60%	47%
S2/ST+7/V-3	GGG	51	23	0.0029	0.0377	47%	34%
S2/ST+7/V-1	GGC	44	15	0.000024	0.0267	78%	66%
S2/ST+7/V1	GGA	42	15	0.0007	0.0198	79%	66%
S2/ST+7/V4	GGC	44	17	0.00018	0.0475	66%	54%
S2/T1/V-4	GTC	55	24	0.0005	0.0654	59%	48%
S2/T1/V-3	GTG	51	21	0.0006	0.0465	47%	35%
S2/T1/V-1	GTC	40	13	0.00009	0.0081	86%	73%
S2/T1/V1	GTA	38	13	0.0006	0.0083	86%	72%
S2/T1/V4	GTC	43	18	0.0008	0.0135	75%	61%
S2/V-4/V-3	GCG	52	24	0.0016	0.0311	48%	35%
S2/V-4/V-1	GCC	54	27	0.0025	0.0541	60%	48%
S2/V-4/V1	GCA	52	27	0.0061	0.0516	60%	49%
S2/V-4/V4	GCC	49	24	0.0053	0.0578	49%	37%
S2/V-3/V-1	GGC	50	24	0.0030	0.0639	47%	36%
S2/V-3/V1	GGA	49	24	0.0057	0.0503	47%	36%
S2/V-3/V4	GGC	49	23	0.0047	0.0520	47%	36%
S2/V-1/V1	GCA	37	15	0.0025	0.0040	87%	73%
S2/V-1/V4	GCC	42	20	0.0045	0.0154	75%	61%
S2/V1/V4	GAC	41	20	0.0085	0.0092	76%	61%
ST+4/ST+7/T1	AGT	48	24	0.0026	0.0002	49%	29%
ST+4/ST+7/V-4	AGC	50	30	0.0427	0.0073	55%	39%
ST+4/ST+7/V-3	AGG	51	28	0.0109	0.0080	55%	38%
ST+4/ST+7/V-1	AGC	47	33	0.1224	0.0166	54%	39%
ST+4/ST+7/V1	AGA	46	32	0.1608	0.0083	55%	39%
ST+4/ST+7/V4	AGC	46	32	0.0521	0.0243	52%	39%
ST+4/T1/V-4	ATC	43	28	0.3649	0.0406	51%	38%



ST+4/T1/V-3	ATG	44	24	0.0681	0.0376	50%	37%
ST+4/T1/V-1	ATC	53	25	0.0016	0.0002	50%	28%
ST+4/T1/V1	ATA	44	32	0.3517	0.0605	50%	38%
ST+4/T1/V4	ATC	50	26	0.0124	0.0047	46%	28%
ST+4/V-4/V-3	ACG	44	31	0.2831	0.1721	57%	48%
ST+4/V-4/V-1	ACC	51	30	0.0296	0.0077	55%	39%
ST+4/V-4/V1	ACA	40	32	0.8356	0.1358	58%	48%
ST+4/V-4/V4	ACC	49	29	0.0864	0.0138	53%	37%
ST+4/V-3/V-1	AGC	50	28	0.0491	0.0206	53%	39%
ST+4/V-3/V1	AGA	43	29	0.1449	0.1805	57%	49%
ST+4/V-3/V4	AGC	50	28	0.0573	0.0224	53%	37%
ST+4/V-1/V1	ACA	50	34	0.1254	0.0176	53%	39%
ST+4/V-1/V4	ACC	49	34	0.0679	0.0146	53%	38%
ST+4/V1/V4	AAC	48	35	0.1921	0.0220	53%	37%
ST+7/T1/V-4	GTC	55	25	0.00022	0.0227	61%	47%
ST+7/T1/V-3	GTG	51	22	0.0007	0.0148	49%	34%
ST+7/T1/V-1	GTC	45	17	0.0008	0.0215	79%	66%
ST+7/T1/V1	GTA	42	17	0.0014	0.0129	80%	66%
ST+7/T1/V4	GTC	46	17	0.000019	0.0725	66%	55%
ST+7/V-4/V-3	GCG	53	29	0.0054	0.3004	54%	48%
ST+7/V-4/V-1	GCC	48	28	0.0079	0.2444	67%	60%
ST+7/V-4/V1	GCA	47	28	0.0120	0.2454	67%	61%
ST+7/V-4/V4	GCC	47	30	0.0254	0.2235	55%	47%
ST+7/V-3/V-1	GGC	51	30	0.0292	0.4391	52%	48%
ST+7/V-3/V1	GGA	50	29	0.0462	0.2883	54%	47%
ST+7/V-3/V4	GGC	50	29	0.0140	0.4155	52%	48%
ST+7/V-1/V1	GCA	31	16	0.0531	0.2946	85%	80%
ST+7/V-1/V4	GCC	41	23	0.0129	0.1933	73%	66%
ST+7/V1/V4	GAC	40	22	0.0222	0.2794	73%	67%
T1/V-4/V-3	TCG	40	30	0.3693	0.6269	52%	49%
T1/V-4/V-1	TCC	57	26	0.0003	0.0377	61%	48%
T1/V-4/V1	TCA	44	33	0.4101	0.4499	64%	60%
T1/V-4/V4	TCC	51	23	0.0042	0.1040	48%	39%
T1/V-3/V-1	TGC	53	23	0.0008	0.0810	46%	35%
T1/V-3/V1	TGA	44	27	0.1445	0.6144	50%	46%
T1/V-3/V4	TGC	52	22	0.0006	0.2228	45%	37%
T1/V-1/V1	TCA	37	16	0.0053	0.0035	88%	73%
T1/V-1/V4	TCC	46	19	0.0003	0.0112	76%	62%
T1/V1/V4	TAC	46	19	0.0030	0.0172	75%	61%
V-4/V-3/V-1	CGC	50	30	0.0107	0.2936	55%	48%
V-4/V-3/V1	CGA	39	32	0.6089	0.6511	57%	60%
V-4/V-3/V4	CGC	49	29	0.0246	0.5371	53%	49%
V-4/V-1/V1	CCA	46	28	0.0151	0.3456	67%	62%
V-4/V-1/V4	CCC	49	31	0.0229	0.2357	55%	48%
V-4/V1/V4	CAC	48	30	0.1233	0.3027	55%	49%
V-3/V-1/V1	GCA	51	31	0.0464	0.5509	52%	49%
V-3/V-1/V4	GCC	51	30	0.0200	0.4976	52%	48%
V-3/V1/V4	GAC	50	29	0.0360	0.5177	52%	47%
V-1/V1/V4	CAC	37	21	0.0289	0.0679	82%	73%

S1/T1/V-1/V1	GTCA	35	13	0.0006	0.0032	88%	73%
S1/T1/V-1/V4	GTCC	45	19	0.0010	0.0127	76%	61%
S1/T1/V1/V4	GTAC	45	19	0.0011	0.0146	76%	62%
S1/V-1/V1/V4	GCAC	36	21	0.0573	0.0619	82%	73%
S2/ST+7/T1/V-4	GGTC	54	24	0.000015	0.0263	60%	46%
S2/ST+7/T1/V-3	GGTG	49	20	0.00014	0.0631	46%	35%
S2/ST+7/T1/V-1	GGTC	46	13	0.000009	0.0325	77%	66%
S2/ST+7/T1/V4	GGTC	46	15	0.000020	0.0448	66%	54%
S2/ST+7/V-4/V-1	GGCC	53	27	0.0049	0.0392	60%	47%
S2/ST+7/V-4/V4	GGCC	46	23	0.0078	0.0271	50%	35%
S2/ST+7/V-3/V-1	GGGC	48	22	0.0033	0.0429	47%	35%
S2/ST+7/V-3/V4	GGGC	47	22	0.0057	0.0461	47%	34%
S2/ST+7/V-1/V4	GGCC	44	17	0.0005	0.0514	66%	54%
S2/T1/V-4/V-1	GTCC	55	24	0.00004	0.0338	60%	48%
S2/T1/V-4/V4	GTCC	50	21	0.00015	0.0775	48%	37%
S2/T1/V-3/V-1	GTGC	51	21	0.00021	0.0882	46%	35%
S2/T1/V-3/V4	GTGC	50	20	0.0007	0.0817	46%	36%
S2/T1/V-1/V4	GTCC	43	18	0.0010	0.0142	75%	61%
S2/V-4/V-1/V4	GCCC	49	24	0.0068	0.0356	50%	37%
S2/V-3/V-1/V4	GGCC	49	23	0.0080	0.0744	47%	36%
ST+7/T1/V-4/V-1	GTCC	55	25	0.00014	0.0251	60%	47%
ST+7/T1/V-4/V4	GTCC	48	21	0.00013	0.0547	48%	36%
ST+7/T1/V-3/V-1	GTGC	51	22	0.0014	0.0528	46%	34%
ST+7/T1/V-3/V4	GTGC	50	21	0.0004	0.0632	46%	35%
ST+7/T1/V-1/V4	GTCC	46	17	0.00006	0.0387	67%	54%
ST+7/V-4/V-1/V4	GCCC	47	30	0.0256	0.2151	55%	47%
ST+7/V-3/V-1/V4	GGCC	50	29	0.0142	0.3916	52%	47%
T1/V-4/V-1/V4	TCCC	51	22	0.0002	0.0564	48%	36%
T1/V-3/V-1/V4	TGCC	52	21	0.0004	0.0913	46%	35%
T1/V-1/V1/V4	TCAC	45	19	0.0004	0.0136	76%	62%
S1/T1/V-1/V1/V4	GTAC	44	19	0.0022	0.0130	76%	62%
S2/ST+7/T1/V-3/V-1	GGTGC	49	20	0.000001	0.0672	46%	35%
S2/ST+7/T1/V-3/V4	GGTGC	48	20	0.00005	0.0714	46%	35%
S2/ST+7/T1/V-1/V4	GGTCC	46	15	0.0005	0.0463	66%	54%
S2/ST+7/V-3/V-1/V4	GGGCC	47	22	0.0040	0.0459	47%	35%
S2/T1/V-3/V-1/V4	GTGCC	50	20	0.0009	0.1091	46%	36%
ST+7/T1/V-3/V-1/V4	GTGCC	50	21	0.0004	0.0590	46%	34%

**TABLE 29 (CON'T)**

BHR US							
SNP(s)	Over- Transmitted Allele or Haplo	T	NT	TD p-value	Case/ Cntl p-value	Case freq	Cntl freq
L-1	G	10	2	0.0386	0.0149	75%	92%
S1	A	6	3	0.5078	0.4980	15%	10%
S2	G	12	7	0.3593	0.0233	54%	75%
ST+4	C	11	9	0.8238	0.5212	35%	43%
ST+7	A	8	3	0.2266	0.6391	29%	24%
T1	T	11	3	0.0574	0.0041	71%	92%
V-4	G	9	6	0.6072	0.6296	29%	23%
V-3	A	12	8	0.5034	0.8311	32%	35%
V-1	A	7	4	0.5488	0.5937	21%	17%
V1	A	1	1	1.0000	1.0000	96%	94%
V4	G	7	5	0.7744	0.6206	25%	21%
L-1/S1	GG	10	6	0.1439	0.0247	62%	82%
L-1/S1	GA	6	3	0.1439	0.7265	13%	10%
L-1/S2	GG	11	7	0.0880	0.0237	54%	75%
L-1/S2	GC	8	4	0.0880	0.5874	21%	16%
L-1/ST+4	GA	13	7	0.0549	0.3954	39%	49%
L-1/ST+4	GC	11	8	0.0549	0.4622	36%	43%
L-1/ST+7	GA	10	3	0.0423	0.5436	29%	24%
L-1/T1	GT	10	3	0.0652	0.0040	71%	92%
L-1/V-4	GC	14	8	0.0624	0.0148	46%	69%
L-1/V-4	GG	9	6	0.0624	0.5008	29%	23%
L-1/V-3	GG	13	8	0.0678	0.2266	43%	57%
L-1/V-3	GA	11	7	0.0678	0.8480	32%	35%
L-1/V-1	GC	11	7	0.1727	0.0149	54%	75%
L-1/V-1	GA	7	4	0.1727	0.5193	21%	17%
L-1/V1	GA	10	3	0.0670	0.0687	71%	86%
L-1/V4	GC	11	5	0.1358	0.0200	50%	71%
S1/S2	GG	11	7	0.1714	0.0215	54%	75%
S1/S2	AC	6	3	0.1714	0.3681	17%	10%
S1/ST+4	AA	6	3	0.5532	0.3858	15%	10%
S1/ST+7	AA	6	3	0.2126	0.2371	19%	10%
S1/ST+7	GA	4	1	0.2126	0.5314	10%	14%
S1/T1	GT	12	7	0.1264	0.0032	56%	82%
S1/T1	AT	6	3	0.1264	0.4192	16%	10%
S1/V-4	GG	9	7	0.4447	0.5289	29%	23%
S1/V-4	AC	6	3	0.4447	0.3904	16%	10%
S1/V-3	GA	11	8	0.5956	0.8127	32%	35%
S1/V-1	AA	6	3	0.7528	0.1235	21%	10%
S1/V1	AA	6	3	0.7528	0.5399	15%	10%
S1/V4	AG	6	3	0.7490	0.1244	20%	10%
S2/ST+4	GC	12	10	0.3910	0.5419	32%	39%

S2/ST+4	GA	10	6	0.3910	0.1169	21%	36%
S2/ST+7	GG	12	10	0.0606	0.0232	46%	68%
S2/ST+7	CA	8	4	0.0606	0.7448	21%	17%
S2/ST+7	GA	4	1	0.0606	0.8389	8%	7%
S2/T1	GT	12	8	0.2307	0.0070	50%	75%
S2/T1	CT	7	4	0.2307	0.4693	22%	17%
S2/V-4	GC	13	9	0.4478	0.0039	25%	52%
S2/V-3	GA	12	8	0.2960	0.8529	32%	35%
S2/V-3	GG	9	6	0.2960	0.0658	21%	40%
S2/V-1	GC	11	7	0.0685	0.0171	54%	75%
S2/V-1	CA	7	3	0.0685	0.5932	21%	17%
S2/V1	GA	11	7	0.3319	0.0245	54%	75%
S2/V4	GC	10	5	0.0860	0.1281	49%	64%
S2/V4	CG	7	3	0.0860	0.1992	21%	10%
ST+4/ST+7	AA	6	3	0.2854	0.6633	18%	14%
ST+4/ST+7	CA	5	1	0.2854	0.9512	11%	10%
ST+4/T1	AT	14	7	0.0878	0.2161	36%	49%
ST+4/V-4	CG	9	7	0.7057	0.5042	29%	23%
ST+4/V-3	CA	12	8	0.5217	0.7999	32%	35%
ST+4/V-1	AA	6	3	0.7772	0.6109	17%	13%
ST+4/V1	CA	11	10	1.0000	0.5851	31%	37%
ST+4/V4	CC	10	8	0.6549	0.4848	26%	33%
ST+4/V4	AG	6	3	0.6549	0.5004	16%	10%
ST+7/T1	GT	11	9	0.0798	0.0139	43%	68%
ST+7/T1	AT	9	3	0.0798	0.5498	29%	24%
ST+7/V-4	AC	8	4	0.2080	0.7519	24%	21%
ST+7/V-4	AG	3	0	0.2080	0.8827	5%	4%
ST+7/V-3	AG	8	4	0.1944	0.8537	21%	19%
ST+7/V-3	AA	3	0	0.1944	0.6506	7%	5%
ST+7/V-1	AA	7	4	0.1853	0.6932	21%	17%
ST+7/V-1	AC	4	1	0.1853	0.9446	7%	7%
ST+7/V1	AA	9	3	0.1854	0.3725	25%	18%
ST+7/V4	AG	7	4	0.2707	0.0589	25%	10%
ST+7/V4	AC	4	1	0.2707	0.1029	4%	14%
T1/V-4	TC	15	8	0.0636	0.0080	43%	69%
T1/V-3	TG	14	8	0.0609	0.1305	39%	57%
T1/V-3	TA	11	8	0.0609	0.8510	32%	35%
T1/V-1	TC	13	8	0.1361	0.0126	50%	75%
T1/V-1	TA	7	4	0.1361	0.5156	21%	17%
T1/V1	TA	12	4	0.0881	0.0242	68%	86%
T1/V4	TC	12	6	0.0983	0.0125	46%	71%
V-4/V-3	GA	9	7	0.7963	0.4999	29%	23%
V-4/V-1	GC	9	7	0.5194	0.5464	29%	23%
V-4/V-1	CA	7	4	0.5194	0.5474	21%	17%
V-4/V1	GA	9	7	0.8946	0.5588	29%	23%
V-4/V4	GC	9	7	0.5087	0.4393	29%	21%
V-4/V4	CG	7	4	0.5087	0.5596	25%	19%
V-3/V-1	AC	11	8	0.5199	0.8201	32%	35%
V-3/V1	AA	11	8	0.8131	0.7778	32%	35%

V-3/V4	AC	9	7	0.6244	0.7957	28%	25%
V-3/V4	GG	7	4	0.6244	0.2110	20%	10%
V-1/V1	AA	6	3	0.7535	0.2876	18%	11%
V-1/V4	AG	7	4	0.7432	0.0976	21%	10%
V1/V4	AG	8	4	0.8769	0.9849	21%	21%
L-1/S1/S2	GGG	10	7	0.3026	0.0233	54%	75%
L-1/S1/S2	GAC	6	3	0.3026	0.1409	21%	10%
L-1/S1/ST+4	GGA	10	7	0.2126	0.0841	23%	39%
L-1/S1/ST+4	GAA	6	3	0.2126	0.4271	16%	10%
L-1/S1/ST+7	GAA	6	3	0.1485	0.2556	19%	10%
L-1/S1/ST+7	GGA	4	1	0.1485	0.5312	10%	14%
L-1/S1/T1	GGT	11	7	0.2071	0.0041	56%	82%
L-1/S1/T1	GAT	6	3	0.2071	0.4294	16%	10%
L-1/S1/V-4	GGG	9	6	0.2011	0.5247	29%	23%
L-1/S1/V-4	GAC	6	3	0.2011	0.4178	17%	10%
L-1/S1/V-3	GGG	10	8	0.2363	0.0545	26%	47%
L-1/S1/V-3	GGA	10	7	0.2363	0.8247	32%	35%
L-1/S1/V-1	GGC	11	7	0.2033	0.0232	54%	75%
L-1/S1/V-1	GAA	6	3	0.2033	0.1393	21%	10%
L-1/S1/V1	GGA	11	7	0.1985	0.0618	59%	76%
L-1/S1/V1	GAA	6	3	0.1985	0.7845	13%	10%
L-1/S1/V4	GGC	11	5	0.1024	0.0405	50%	71%
L-1/S1/V4	GAG	6	3	0.1024	0.1481	20%	10%
L-1/S2/ST+4	GGC	11	9	0.2378	0.5646	32%	39%
L-1/S2/ST+4	GGA	9	6	0.2378	0.1106	21%	36%
L-1/S2/ST+7	GCA	8	4	0.1297	0.4450	21%	17%
L-1/S2/ST+7	GGA	4	1	0.1297	0.9987	7%	7%
L-1/S2/T1	GGT	11	8	0.3158	0.0157	50%	75%
L-1/S2/T1	GCT	7	4	0.3158	0.5647	21%	17%
L-1/S2/V-4	GGC	11	9	0.1654	0.0058	25%	52%
L-1/S2/V-4	GGG	9	6	0.1654	0.5142	29%	23%
L-1/S2/V-4	GCC	8	5	0.1654	0.5923	21%	16%
L-1/S2/V-3	GGA	11	7	0.1705	0.8379	32%	35%
L-1/S2/V-1	GGC	10	7	0.1385	0.0203	54%	75%
L-1/S2/V-1	GCA	7	3	0.1385	0.5665	21%	17%
L-1/S2/V1	GGA	10	7	0.2633	0.0187	54%	75%
L-1/S2/V4	GGC	10	5	0.1345	0.1646	50%	64%
L-1/S2/V4	GCG	7	3	0.1345	0.1112	21%	10%
L-1/ST+4/ST+7	GAG	10	7	0.0921	0.1730	21%	35%
L-1/ST+4/ST+7	GAA	6	3	0.0921	0.6556	18%	14%
L-1/ST+4/ST+7	GCA	5	1	0.0921	0.9399	11%	10%
L-1/ST+4/T1	GAT	13	7	0.1663	0.2104	36%	49%
L-1/ST+4/V-4	GAC	12	7	0.1002	0.2973	39%	49%
L-1/ST+4/V-4	GCG	9	6	0.1002	0.5136	29%	23%
L-1/ST+4/V-3	GCA	11	7	0.0916	0.8011	32%	35%
L-1/ST+4/V-3	GAG	11	7	0.0916	0.3000	39%	49%
L-1/ST+4/V-1	GAC	10	7	0.2993	0.1207	21%	36%
L-1/ST+4/V-1	GAA	6	3	0.2993	0.5995	17%	13%
L-1/ST+4/V1	GAA	13	7	0.1791	0.4056	40%	49%

L-1/ST+4/V4	GCC	10	7	0.2386	0.6365	28%	33%
L-1/ST+4/V4	GAC	10	7	0.2386	0.1054	22%	39%
L-1/ST+4/V4	GAG	6	3	0.2386	0.4631	17%	10%
L-1/ST+7/T1	GAT	9	3	0.1202	0.5425	29%	24%
L-1/ST+7/V-4	GAC	8	4	0.0911	0.6434	25%	20%
L-1/ST+7/V-4	GAG	3	0	0.0911	0.9804	4%	4%
L-1/ST+7/V-3	GGG	9	7	0.0814	0.0802	21%	38%
L-1/ST+7/V-3	GAG	8	4	0.0814	0.7532	21%	19%
L-1/ST+7/V-3	GAA	3	0	0.0814	0.7508	7%	5%
L-1/ST+7/V-1	GAA	7	4	0.1443	0.7075	21%	17%
L-1/ST+7/V-1	GAC	4	1	0.1443	0.8154	7%	7%
L-1/ST+7/V1	GAA	9	3	0.1225	0.3806	25%	18%
L-1/ST+7/V4	GGC	9	6	0.1511	0.2643	46%	58%
L-1/ST+7/V4	GAG	7	4	0.1511	0.0640	25%	10%
L-1/ST+7/V4	GAC	4	1	0.1511	0.1057	4%	14%
L-1/T1/V-4	GTC	13	8	0.1270	0.0079	43%	69%
L-1/T1/V-4	GTG	9	6	0.1270	0.5006	29%	23%
L-1/T1/V-3	GTG	13	8	0.1276	0.1332	39%	57%
L-1/T1/V-3	GTA	10	7	0.1276	0.8489	32%	35%
L-1/T1/V-1	GTC	12	8	0.2273	0.0120	50%	75%
L-1/T1/V-1	GTA	7	4	0.2273	0.5199	21%	17%
L-1/T1/V1	GTA	11	4	0.1167	0.0203	68%	86%
L-1/T1/V4	GTC	12	6	0.1800	0.0141	46%	71%
L-1/V-4/V-3	GCG	14	8	0.0924	0.2067	43%	57%
L-1/V-4/V-1	GGC	9	6	0.2204	0.5136	29%	23%
L-1/V-4/V-1	GCA	7	4	0.2204	0.5764	21%	17%
L-1/V-4/V1	GCA	11	7	0.2247	0.0399	43%	63%
L-1/V-4/V1	GGA	9	6	0.2247	0.5072	29%	23%
L-1/V-4/V4	GGC	9	6	0.2377	0.4240	29%	21%
L-1/V-4/V4	GCC	9	7	0.2377	0.0082	21%	50%
L-1/V-3/V-1	GAC	10	7	0.2390	0.8379	32%	35%
L-1/V-3/V1	GGA	11	7	0.2200	0.2475	39%	51%
L-1/V-3/V1	GAA	10	7	0.2200	0.8313	32%	35%
L-1/V-3/V4	GGC	9	7	0.2916	0.0239	22%	46%
L-1/V-3/V4	GAC	9	6	0.2916	0.7526	28%	25%
L-1/V-3/V4	GGG	7	4	0.2916	0.2113	21%	10%
L-1/V-1/V1	GCA	11	7	0.2014	0.0212	54%	75%
L-1/V-1/V1	GAA	6	3	0.2014	0.3427	18%	11%
L-1/V-1/V4	GCC	11	5	0.1059	0.1632	50%	64%
L-1/V1/V4	GAC	11	5	0.1647	0.1348	50%	65%
S1/S2/ST+4	GGA	10	6	0.1989	0.1184	21%	36%
S1/S2/ST+4	ACA	6	3	0.1989	0.5764	15%	10%
S1/S2/ST+7	GGG	12	10	0.1389	0.0326	46%	68%
S1/S2/ST+7	ACA	6	3	0.1389	0.1418	21%	10%
S1/S2/ST+7	GGA	4	1	0.1389	0.9725	7%	7%
S1/S2/T1	GGT	12	8	0.2876	0.0103	50%	75%
S1/S2/T1	ACT	6	3	0.2876	0.1376	21%	10%
S1/S2/V-4	GGC	12	9	0.2029	0.0048	25%	52%
S1/S2/V-4	ACC	6	3	0.2029	0.3800	17%	10%

S1/S2/V-3	GGA	11	8	0.2190	0.8456	32%	35%
S1/S2/V-3	GGG	9	6	0.2190	0.0661	21%	40%
S1/S2/V-1	GGC	11	7	0.0939	0.0255	54%	75%
S1/S2/V-1	ACA	6	3	0.0939	0.1379	21%	10%
S1/S2/V1	GGA	11	7	0.1008	0.0185	54%	75%
S1/S2/V1	ACA	6	3	0.1008	0.3821	16%	10%
S1/S2/V4	GGC	10	5	0.1038	0.1733	50%	64%
S1/S2/V4	ACG	6	3	0.1038	0.0844	21%	10%
S1/ST+4/ST+7	AAA	6	3	0.4445	0.3326	18%	10%
S1/ST+4/ST+7	GCA	4	1	0.4445	0.9485	11%	13%
S1/ST+4/T1	GAT	11	7	0.1871	0.0407	19%	39%
S1/ST+4/T1	AAT	6	3	0.1871	0.4140	16%	10%
S1/ST+4/V-4	GCG	9	7	0.5933	0.5154	29%	23%
S1/ST+4/V-4	AAC	6	3	0.5933	0.4205	15%	10%
S1/ST+4/V-3	GCA	11	8	0.7614	0.8020	32%	35%
S1/ST+4/V-1	AAA	6	3	0.7762	0.3677	17%	10%
S1/ST+4/V1	AAA	6	3	0.7718	0.4017	15%	10%
S1/ST+4/V4	GCC	10	8	0.6440	0.6781	28%	32%
S1/ST+4/V4	AAG	6	3	0.6440	0.2995	18%	10%
S1/ST+7/T1	GGT	12	10	0.1251	0.0121	43%	68%
S1/ST+7/T1	AAT	6	3	0.1251	0.2457	19%	10%
S1/ST+7/T1	GAT	4	1	0.1251	0.5289	10%	14%
S1/ST+7/V-4	AAC	6	3	0.3865	0.1522	21%	10%
S1/ST+7/V-4	GAG	3	0	0.3865	0.6145	7%	4%
S1/ST+7/V-3	AAG	6	3	0.3802	0.1690	21%	10%
S1/ST+7/V-3	GAA	3	0	0.3802	0.7005	7%	5%
S1/ST+7/V-1	AAA	6	3	0.2654	0.1241	21%	10%
S1/ST+7/V-1	GAC	4	1	0.2654	0.7975	7%	7%
S1/ST+7/V1	AAA	6	3	0.2668	0.3794	17%	10%
S1/ST+7/V1	GAA	4	1	0.2668	0.7833	8%	7%
S1/ST+7/V4	AAG	6	3	0.4111	0.1435	20%	10%
S1/ST+7/V4	GAC	4	1	0.4111	0.1001	4%	14%
S1/T1/V-4	GTC	15	11	0.1095	0.0009	26%	59%
S1/T1/V-4	ATC	6	3	0.1095	0.4035	17%	10%
S1/T1/V-3	GTG	12	8	0.1098	0.0257	22%	47%
S1/T1/V-3	GTA	11	8	0.1098	0.8343	32%	35%
S1/T1/V-1	GTC	13	8	0.1711	0.0141	50%	75%
S1/T1/V-1	ATA	6	3	0.1711	0.1349	21%	10%
S1/T1/V1	GTA	13	8	0.1773	0.0164	53%	76%
S1/T1/V1	ATA	6	3	0.1773	0.4696	15%	10%
S1/T1/V4	GTC	12	6	0.1183	0.0134	46%	71%
S1/V-4/V-3	GGA	9	7	0.5859	0.5167	29%	23%
S1/V-4/V-3	ACG	6	3	0.5859	0.4043	16%	10%
S1/V-4/V-1	GGC	9	7	0.6329	0.5434	29%	23%
S1/V-4/V-1	ACA	6	3	0.6329	0.1450	21%	10%
S1/V-4/V1	GGA	9	7	0.6381	0.5566	29%	23%
S1/V-4/V1	ACA	6	3	0.6381	0.4090	15%	10%
S1/V-4/V4	GGC	9	7	0.6033	0.5804	25%	20%
S1/V-4/V4	ACG	6	3	0.6033	0.1356	21%	10%

S1/V-3/V-1	GAC	11	8	0.7640	0.8163	32%	35%
S1/V-3/V1	GAA	11	8	0.7627	0.8094	32%	35%
S1/V-3/V4	GAC	9	7	0.7586	0.6843	29%	25%
S1/V-3/V4	AGG	6	3	0.7586	0.1524	21%	10%
S1/V-1/V1	AAA	6	3	0.7503	0.3480	18%	10%
S1/V-1/V4	AAG	6	3	0.8625	0.0973	21%	10%
S1/V1/V4	AAG	6	3	0.8579	0.3348	17%	10%
S2/ST+4/ST+7	GAG	10	6	0.1001	0.1154	21%	36%
S2/ST+4/ST+7	CAA	6	3	0.1001	0.5817	18%	14%
S2/ST+4/ST+7	GCA	4	1	0.1001	0.9197	7%	7%
S2/ST+4/T1	GAT	10	6	0.4371	0.0491	16%	36%
S2/ST+4/V-4	GAC	9	6	0.5616	0.0845	21%	37%
S2/ST+4/V-4	GCG	9	7	0.5616	0.4981	29%	23%
S2/ST+4/V-3	GCA	12	8	0.2961	0.7975	32%	35%
S2/ST+4/V-3	GAG	9	6	0.2961	0.0793	21%	38%
S2/ST+4/V-1	GAC	10	6	0.2008	0.1249	21%	36%
S2/ST+4/V-1	CAA	6	3	0.2008	0.5726	17%	13%
S2/ST+4/V1	GAA	10	6	0.6444	0.0511	21%	38%
S2/ST+4/V4	GAC	10	6	0.2614	0.1487	21%	36%
S2/ST+4/V4	GCC	10	8	0.2614	0.9147	28%	29%
S2/ST+4/V4	CAG	6	3	0.2614	0.4058	17%	10%
S2/ST+7/T1	GGT	12	10	0.2028	0.0089	43%	68%
S2/ST+7/T1	CAT	7	4	0.2028	0.4525	21%	17%
S2/ST+7/T1	GAT	4	1	0.2028	0.8165	7%	7%
S2/ST+7/V-4	GGC	12	9	0.0594	0.0077	25%	49%
S2/ST+7/V-4	CAC	8	4	0.0594	0.7005	21%	18%
S2/ST+7/V-4	GAG	3	0	0.0594	0.5648	7%	4%
S2/ST+7/V-3	GGG	9	6	0.0550	0.0877	21%	38%
S2/ST+7/V-3	CAG	8	4	0.0550	0.6913	21%	18%
S2/ST+7/V-3	GAA	3	0	0.0550	0.5504	7%	4%
S2/ST+7/V-1	GGC	12	10	0.1020	0.0237	46%	68%
S2/ST+7/V-1	CAA	7	4	0.1020	0.5188	21%	17%
S2/ST+7/V-1	GAC	4	1	0.1020	0.9992	7%	7%
S2/ST+7/V1	GGA	12	10	0.1445	0.0212	46%	68%
S2/ST+7/V1	CAA	6	3	0.1445	0.4370	17%	11%
S2/ST+7/V1	GAA	4	1	0.1445	0.8003	8%	7%
S2/ST+7/V4	GGC	9	6	0.1309	0.2843	46%	57%
S2/ST+7/V4	CAG	7	4	0.1309	0.1441	21%	10%
S2/ST+7/V4	GAC	4	1	0.1309	0.5102	4%	7%
S2/T1/V-4	GTC	13	9	0.2349	0.0011	21%	52%
S2/T1/V-3	GTA	11	8	0.2115	0.8428	32%	35%
S2/T1/V-3	GTG	10	6	0.2115	0.0263	17%	40%
S2/T1/V-1	GTC	12	8	0.1485	0.0113	50%	75%
S2/T1/V-1	CTA	7	3	0.1485	0.5980	21%	17%
S2/T1/V1	GTA	12	8	0.2210	0.0055	50%	75%
S2/T1/V4	GTC	11	6	0.1797	0.0753	46%	64%
S2/T1/V4	CTG	7	3	0.1797	0.1115	21%	10%
S2/V-4/V-3	GGA	9	7	0.5762	0.5069	29%	23%
S2/V-4/V-3	GCG	9	6	0.5762	0.0478	21%	41%



S2/V-4/V-1	GCC	12	9	0.1580	0.0063	25%	52%
S2/V-4/V-1	CCA	7	4	0.1580	0.5277	21%	17%
S2/V-4/V1	GCA	12	9	0.7370	0.0048	25%	52%
S2/V-4/V4	GGC	9	7	0.2348	0.4372	29%	20%
S2/V-4/V4	GCC	9	6	0.2348	0.0258	21%	44%
S2/V-4/V4	CCG	7	4	0.2348	0.2190	21%	10%
S2/V-3/V-1	GAC	11	8	0.1628	0.8445	32%	35%
S2/V-3/V-1	GGC	9	6	0.1628	0.0670	21%	40%
S2/V-3/V1	GAA	11	8	0.4978	0.8474	32%	35%
S2/V-3/V1	GGA	9	6	0.4978	0.0710	21%	40%
S2/V-3/V4	GGC	9	6	0.2339	0.0726	21%	40%
S2/V-3/V4	GAC	9	7	0.2339	0.7349	28%	24%
S2/V-3/V4	CGG	7	4	0.2339	0.1648	21%	10%
S2/V-1/V1	GCA	11	7	0.0947	0.0206	54%	75%
S2/V-1/V1	CAA	6	3	0.0947	0.2679	18%	11%
S2/V-1/V4	GCC	10	5	0.0899	0.1609	50%	64%
S2/V-1/V4	CAG	7	3	0.0899	0.1068	21%	10%
S2/V1/V4	GAC	10	5	0.1035	0.1297	49%	64%
S2/V1/V4	CAG	6	3	0.1035	0.3487	17%	10%
ST+4/ST+7/T1	AGT	11	7	0.1446	0.0827	17%	35%
ST+4/ST+7/T1	AAT	6	3	0.1446	0.6652	18%	14%
ST+4/ST+7/T1	CAT	4	1	0.1446	0.9429	11%	10%
ST+4/ST+7/V-4	AAC	6	3	0.4032	0.5870	18%	13%
ST+4/ST+7/V-4	CAG	3	0	0.4032	0.9669	4%	3%
ST+4/ST+7/V-3	AAG	6	3	0.2972	0.4444	18%	12%
ST+4/ST+7/V-3	CAA	3	0	0.2972	0.7059	7%	5%
ST+4/ST+7/V-1	AAA	6	3	0.6047	0.4697	18%	12%
ST+4/ST+7/V-1	CAC	4	1	0.6047	0.8515	7%	7%
ST+4/ST+7/V1	AAA	6	3	0.6057	0.5841	18%	14%
ST+4/ST+7/V1	CAA	4	1	0.6057	0.6623	7%	4%
ST+4/ST+7/V4	AAG	6	3	0.7131	0.3212	18%	10%
ST+4/ST+7/V4	CAC	4	1	0.7131	0.2374	4%	12%
ST+4/T1/V-4	ATC	14	7	0.0896	0.1483	35%	49%
ST+4/T1/V-3	ATG	13	7	0.0747	0.1532	35%	49%
ST+4/T1/V-3	CTA	11	8	0.0747	0.7994	32%	35%
ST+4/T1/V-1	ATC	11	7	0.2564	0.0531	17%	38%
ST+4/T1/V-1	ATA	6	3	0.2564	0.5834	17%	13%
ST+4/T1/V1	ATA	14	7	0.1508	0.2372	36%	49%
ST+4/T1/V4	ATC	11	7	0.2473	0.0413	18%	39%
ST+4/T1/V4	ATG	6	3	0.2473	0.4411	17%	10%
ST+4/V-4/V-3	CGA	9	7	0.8063	0.5127	29%	23%
ST+4/V-4/V-1	CGC	9	7	0.7628	0.5341	29%	23%
ST+4/V-4/V-1	ACA	6	3	0.7628	0.4519	18%	12%
ST+4/V-4/V1	CGA	9	7	0.9682	0.5060	29%	23%
ST+4/V-4/V4	CGC	9	7	0.5974	0.4499	29%	22%
ST+4/V-4/V4	ACG	6	3	0.5974	0.2215	18%	9%
ST+4/V-3/V-1	CAC	11	8	0.7643	0.8090	32%	35%
ST+4/V-3/V1	CAA	11	8	0.8166	0.7760	32%	35%
ST+4/V-3/V4	CAC	9	7	0.7598	0.8562	27%	26%

ST+4/V-3/V4	AGG	6	3	0.7598	0.4921	17%	11%
ST+4/V-1/V1	AAA	6	3	0.7811	0.2975	18%	11%
ST+4/V-1/V4	CCC	10	8	0.8247	0.9301	26%	27%
ST+4/V-1/V4	AAG	6	3	0.8247	0.3737	17%	10%
ST+4/V1/V4	CAC	10	8	0.8323	0.9278	26%	27%
ST+4/V1/V4	AAG	6	3	0.8323	0.5145	17%	11%
ST+7/T1/V-4	GTC	14	10	0.0657	0.0004	18%	49%
ST+7/T1/V-4	ATC	7	4	0.0657	0.6332	25%	20%
ST+7/T1/V-4	ATG	3	0	0.0657	0.9962	4%	4%
ST+7/T1/V-3	GTG	11	7	0.0616	0.0293	18%	38%
ST+7/T1/V-3	ATG	7	4	0.0616	0.7485	21%	19%
ST+7/T1/V-3	ATA	3	0	0.0616	0.7488	7%	5%
ST+7/T1/V-1	GTC	12	10	0.1340	0.0116	43%	68%
ST+7/T1/V-1	ATA	7	4	0.1340	0.7108	21%	17%
ST+7/T1/V-1	ATC	4	1	0.1340	0.9202	7%	7%
ST+7/T1/V1	GTA	11	9	0.1117	0.0147	43%	68%
ST+7/T1/V1	ATA	9	3	0.1117	0.3722	25%	18%
ST+7/T1/V4	GTC	9	6	0.1714	0.1334	43%	58%
ST+7/T1/V4	ATG	7	4	0.1714	0.0579	25%	10%
ST+7/T1/V4	ATC	4	1	0.1714	0.1020	4%	14%
ST+7/V-4/V-3	ACG	8	4	0.2909	0.8569	21%	20%
ST+7/V-4/V-3	AGA	3	0	0.2909	0.9860	4%	4%
ST+7/V-4/V-1	ACA	7	4	0.2838	0.4770	21%	17%
ST+7/V-4/V-1	AGC	3	0	0.2838	0.5085	7%	4%
ST+7/V-4/V1	ACA	6	3	0.3891	0.4615	20%	14%
ST+7/V-4/V1	AGA	3	0	0.3891	0.8427	5%	3%
ST+7/V-4/V4	ACG	7	4	0.3935	0.0336	25%	10%
ST+7/V-4/V4	AGC	3	0	0.3935	0.8772	4%	4%
ST+7/V-3/V-1	AGA	7	4	0.2793	0.4593	21%	17%
ST+7/V-3/V-1	AAC	3	0	0.2793	0.4629	7%	5%
ST+7/V-3/V1	AGA	6	3	0.3791	0.5308	18%	13%
ST+7/V-3/V1	AAA	3	0	0.3791	0.6434	7%	5%
ST+7/V-3/V4	AGG	7	4	0.3958	0.1148	21%	10%
ST+7/V-3/V4	AAC	3	0	0.3958	0.7591	4%	6%
ST+7/V-1/V1	AAA	6	3	0.2624	0.2770	18%	11%
ST+7/V-1/V1	ACA	4	1	0.2624	0.9613	7%	7%
ST+7/V-1/V4	AAG	7	4	0.2692	0.1040	21%	10%
ST+7/V-1/V4	ACC	4	1	0.2692	0.4362	4%	7%
ST+7/V1/V4	AAG	6	3	0.4070	0.1140	21%	10%
ST+7/V1/V4	AAC	4	1	0.4070	0.3731	4%	8%
T1/V-4/V-3	TCG	15	8	0.0890	0.1231	39%	57%
T1/V-4/V-1	TCC	14	10	0.1138	0.0012	21%	52%
T1/V-4/V-1	TCA	7	4	0.1138	0.5659	21%	17%
T1/V-4/V1	TCA	14	7	0.0752	0.0110	39%	63%
T1/V-4/V4	TCC	11	7	0.1062	0.0024	18%	50%
T1/V-4/V4	TCG	7	4	0.1062	0.5389	25%	19%
T1/V-3/V-1	TAC	11	8	0.1125	0.8461	32%	35%
T1/V-3/V-1	TGC	11	7	0.1125	0.0306	18%	40%
T1/V-3/V1	TGA	13	7	0.0775	0.1668	36%	51%

T1/V-3/V1	TAA	11	8	0.0775	0.8252	32%	35%
T1/V-3/V4	TGC	11	7	0.1579	0.0117	18%	46%
T1/V-3/V4	TGG	7	4	0.1579	0.2067	21%	10%
T1/V-1/V1	TCA	13	8	0.1684	0.0133	50%	75%
T1/V-1/V1	TAA	6	3	0.1684	0.3397	18%	11%
T1/V-1/V4	TCC	12	6	0.1217	0.0826	46%	64%
T1/V-1/V4	TAG	7	4	0.1217	0.1260	21%	10%
T1/V1/V4	TAC	12	6	0.1664	0.0574	46%	65%
V-4/V-3/V-1	GAC	9	7	0.6245	0.5090	29%	23%
V-4/V-3/V-1	CGA	7	4	0.6245	0.5213	21%	17%
V-4/V-3/V1	GAA	9	7	0.9672	0.5062	29%	23%
V-4/V-3/V4	GAC	9	7	0.6198	0.4331	29%	22%
V-4/V-3/V4	CGG	7	4	0.6198	0.1307	21%	10%
V-4/V-1/V1	GCA	9	7	0.6385	0.5418	29%	23%
V-4/V-1/V1	CAA	6	3	0.6385	0.2754	18%	11%
V-4/V-1/V4	GCC	9	7	0.6256	0.6165	25%	20%
V-4/V-1/V4	CAG	7	4	0.6256	0.1272	21%	10%
V-4/V1/V4	GAC	9	7	0.6303	0.4980	29%	21%
V-4/V1/V4	CAG	6	3	0.6303	0.8171	21%	19%
V-3/V-1/V1	ACA	11	8	0.7592	0.8098	32%	35%
V-3/V-1/V4	ACC	9	7	0.6202	0.6072	29%	24%
V-3/V-1/V4	GAG	7	4	0.6202	0.1310	21%	10%
V-3/V1/V4	AAC	9	7	0.7614	0.8032	27%	25%
V-3/V1/V4	GAG	6	3	0.7614	0.4394	17%	10%
V-1/V1/V4	AAG	6	3	0.8564	0.3224	18%	10%
S1/T1/V-1/V1	GTCA	13	8	0.1790	0.0127	50%	75%
S1/T1/V-1/V1	ATAA	6	3	0.1790	0.3704	18%	10%
S1/T1/V-1/V4	GTCC	12	6	0.1823	0.0812	46%	64%
S1/T1/V-1/V4	ATAG	6	3	0.1823	0.1256	21%	10%
S1/T1/V1/V4	GTAC	12	6	0.1758	0.0704	46%	65%
S1/T1/V1/V4	ATAG	6	3	0.1758	0.3261	17%	10%
S1/V-1/V1/V4	AAAG	6	3	0.8570	0.3023	18%	10%
S2/ST+7/T1/V-4	GGTC	13	9	0.1205	0.0014	21%	49%
S2/ST+7/T1/V-4	CATC	7	4	0.1205	0.4692	21%	17%
S2/ST+7/T1/V-4	GATG	3	0	0.1205	0.5660	7%	4%
S2/ST+7/T1/V-3	GGTG	10	6	0.1048	0.0332	18%	38%
S2/ST+7/T1/V-3	CATG	7	4	0.1048	0.4842	21%	17%
S2/ST+7/T1/V-3	GATA	3	0	0.1048	0.4934	7%	5%
S2/ST+7/T1/V-1	GGTC	12	10	0.2017	0.0116	43%	68%
S2/ST+7/T1/V-1	CATA	7	4	0.2017	0.5031	21%	17%
S2/ST+7/T1/V-1	GATC	4	1	0.2017	0.9998	7%	7%
S2/ST+7/T1/V4	GGTC	9	6	0.2571	0.1649	43%	57%
S2/ST+7/T1/V4	CATG	7	4	0.2571	0.1102	21%	10%
S2/ST+7/T1/V4	GATC	4	1	0.2571	0.4225	4%	7%
S2/ST+7/V-4/V-1	GGCC	12	9	0.0903	0.0064	25%	49%
S2/ST+7/V-4/V-1	CACA	7	4	0.0903	0.5197	21%	17%
S2/ST+7/V-4/V-1	GAGC	3	0	0.0903	0.6054	7%	4%
S2/ST+7/V-4/V4	GGCC	9	6	0.1321	0.1216	21%	38%
S2/ST+7/V-4/V4	CACG	7	4	0.1321	0.2038	21%	9%

S2/ST+7/V-4/V4	GAGC	3	0	0.1321	0.8073	4%	3%
S2/ST+7/V-3/V-1	GGGC	9	6	0.0854	0.0859	21%	38%
S2/ST+7/V-3/V-1	CAGA	7	4	0.0854	0.5711	21%	17%
S2/ST+7/V-3/V-1	GAAC	3	0	0.0854	0.5257	7%	5%
S2/ST+7/V-3/V4	GGGC	9	6	0.1353	0.0912	21%	38%
S2/ST+7/V-3/V4	CAGG	7	4	0.1353	0.1234	21%	10%
S2/ST+7/V-3/V4	GAAC	3	0	0.1353	0.9107	4%	5%
S2/ST+7/V-1/V4	GGCC	9	6	0.1370	0.2638	46%	57%
S2/ST+7/V-1/V4	CAAG	7	4	0.1370	0.1087	21%	10%
S2/ST+7/V-1/V4	GACC	4	1	0.1370	0.4474	4%	7%
S2/T1/V-4/V-1	GTCC	13	9	0.2102	0.0016	21%	52%
S2/T1/V-4/V-1	CTCA	7	4	0.2102	0.5226	21%	17%
S2/T1/V-4/V4	GTCC	10	6	0.2627	0.0109	18%	44%
S2/T1/V-4/V4	GTGC	9	7	0.2627	0.4494	29%	21%
S2/T1/V-4/V4	CTCG	7	4	0.2627	0.1413	21%	10%
S2/T1/V-3/V-1	GTAC	11	8	0.1925	0.8423	32%	35%
S2/T1/V-3/V-1	GTGC	10	6	0.1925	0.0283	18%	40%
S2/T1/V-3/V4	GTGC	10	6	0.2683	0.0269	18%	40%
S2/T1/V-3/V4	GTAC	9	7	0.2683	0.5901	29%	24%
S2/T1/V-3/V4	CTGG	7	4	0.2683	0.1433	21%	10%
S2/T1/V-1/V4	GTCC	11	6	0.1840	0.0690	46%	64%
S2/T1/V-1/V4	CTAG	7	3	0.1840	0.1045	21%	10%
S2/V-4/V-1/V4	GGCC	9	7	0.2385	0.4472	29%	21%
S2/V-4/V-1/V4	GCCC	9	6	0.2385	0.0324	21%	44%
S2/V-4/V-1/V4	CCAG	7	4	0.2385	0.1338	21%	10%
S2/V-3/V-1/V4	GGCC	9	6	0.2354	0.0733	21%	40%
S2/V-3/V-1/V4	GACC	9	7	0.2354	0.5871	29%	24%
S2/V-3/V-1/V4	CGAG	7	4	0.2354	0.1401	21%	10%
ST+7/T1/V-4/V-1	GTCC	14	10	0.0619	0.0022	21%	49%
ST+7/T1/V-4/V-1	ATCA	7	4	0.0619	0.5546	21%	17%
ST+7/T1/V-4/V-1	ATGC	3	0	0.0619	0.5925	7%	4%
ST+7/T1/V-4/V4	GTCC	11	7	0.0947	0.0192	18%	42%
ST+7/T1/V-4/V4	ATCG	7	4	0.0947	0.0318	25%	10%
ST+7/T1/V-4/V4	ATGC	3	0	0.0947	0.8591	4%	5%
ST+7/T1/V-3/V-1	GTGC	11	7	0.0571	0.0374	18%	38%
ST+7/T1/V-3/V-1	ATGA	7	4	0.0571	0.5613	21%	17%
ST+7/T1/V-3/V-1	ATAC	3	0	0.0571	0.5391	7%	5%
ST+7/T1/V-3/V4	GTGC	11	7	0.0948	0.0300	18%	39%
ST+7/T1/V-3/V4	ATGG	7	4	0.0948	0.1561	21%	10%
ST+7/T1/V-3/V4	ATAC	3	0	0.0948	0.7539	4%	6%
ST+7/T1/V-1/V4	GTCC	9	6	0.1762	0.1664	43%	57%
ST+7/T1/V-1/V4	ATAG	7	4	0.1762	0.1243	21%	10%
ST+7/T1/V-1/V4	ATCC	4	1	0.1762	0.4573	4%	7%
ST+7/V-4/V-1/V4	ACAG	7	4	0.3902	0.1228	21%	10%
ST+7/V-4/V-1/V4	AGCC	3	0	0.3902	0.8237	4%	4%
ST+7/V-3/V-1/V4	AGAG	7	4	0.3916	0.1102	21%	10%
ST+7/V-3/V-1/V4	AACC	3	0	0.3916	0.9346	4%	5%
T1/V-4/V-1/V4	TCCC	11	7	0.1616	0.0125	18%	44%
T1/V-4/V-1/V4	TCAG	7	4	0.1616	0.1622	21%	10%

T1/V-3/V-1/V4	TGCC	11	7	0.1585	0.0313	18%	40%
T1/V-3/V-1/V4	TGAG	7	4	0.1585	0.1588	21%	10%
T1/V-1/V1/V4	TCAC	12	6	0.1846	0.0819	46%	64%
T1/V-1/V1/V4	TAAG	6	3	0.1846	0.3021	18%	10%
S1/T1/V-1/V1/V4	GTCC	12	6	0.1773	0.0753	46%	64%
S1/T1/V-1/V1/V4	ATAAG	6	3	0.1773	0.2896	18%	10%
S2/ST+7/T1/V-3/V-1	GGTGC	10	6	0.0953	0.0363	18%	38%
S2/ST+7/T1/V-3/V-1	CATGA	7	4	0.0953	0.5268	21%	17%
S2/ST+7/T1/V-3/V4	CATGG	10	6	0.1455	0.1222	21%	10%
S2/ST+7/T1/V-3/V4	GGTGC	7	4	0.1455	0.0369	18%	38%
S2/ST+7/T1/V-1/V4	CATAG	9	6	0.2368	0.1086	21%	10%
S2/ST+7/T1/V-1/V4	GGTCC	7	4	0.2368	0.1692	43%	57%
S2/ST+7/V-3/V-1/V4	GGGCC	9	6	0.1569	0.0898	21%	38%
S2/ST+7/V-3/V-1/V4	CAGAG	7	4	0.1569	0.1229	21%	10%
S2/T1/V-3/V-1/V4	GTGCC	10	6	0.2753	0.0285	18%	40%
S2/T1/V-3/V-1/V4	CTGAG	7	4	0.2753	0.1351	21%	10%
ST+7/T1/V-3/V-1/V4	GTGCC	11	7	0.0950	0.0424	18%	38%
ST+7/T1/V-3/V-1/V4	ATGAG	7	4	0.0950	0.1430	21%	10%

#### EXAMPLE 15: Attributable Risk Assessment

The frequency of a functional polymorphism and the relative risk of the heterozygote and homozygote (at-risk) genotypes can be used to evaluate the attributable fraction (M.J. Khoury et al., 1993, *Fundamentals of Genetic Epidemiology*, J.L. Kelsey et al., (eds), *Monographs in Epidemiology and Biostatistics*, Oxford University Press, New York, NY, Section 3, p. 74-77) or attributable risk in the population. An attributable fraction of 25% would mean that if the population were monomorphic for the protective allele, the prevalence of the trait would be 25% lower.

The formula for the attributable fraction is:

$$\text{Attributable fraction} = \frac{(1-f)^2 + 2f(1-f)\gamma + f^2\eta - 1}{(1-f)^2 + 2f(1-f)\gamma + f^2\eta}$$

where  $f$  is the allele frequency,  $\gamma$  is the relative risk of the heterozygote genotype over the wild type homozygote, and  $\eta$  is the risk of the homozygote mutant over the wild type homozygote. This approach requires the estimation of  $f$ ,  $\gamma$  and  $\eta$ . Ideally these quantities should be estimated in an epidemiological sample.

For this study, a genome scan with affected sibling pairs was employed,

followed by association study using IBD = 2 individuals as cases in the case/control comparison. This study design offered maximum power to detect linkage and association. However, it did not provide estimates of the required parameters, namely 1) the relative risk (or odds ratio) of the genotype/allele for most SNPs or haplotypes; and 2) the frequency of the SNP in the general population. In a recent paper, researchers used the data from TDT analysis to estimate allele and genotype relative risks assuming a multiplicative model or  $\eta = \gamma^2$  (D. Altshuler et al., 2000, *Nature Genetics* **26**:76-80). In accordance with this method, the mutant homozygote was predicted to carry a relative risk equal to the square of the risk for the heterozygote.

To overcome some of the difficulties associated with a case/control design (see above), the data obtained from typing eleven SNPs in Gene 216 on the entire population were used to estimate the relative risk of these eleven SNPs. The analysis was not limited to the subset of IBD = 2 individuals. The data from the TDT obtained by using the first asthmatic sibling per family were used. Because of the limited number of informative matings in the TDT analysis, a multiplicative model for the genotype relative risk was used as in Altshuler et al., i.e.  $\eta = \gamma^2$ . By using the control population to estimate allele frequencies, the attributable risk may have been underestimated. Based on this, the attributable risk was computed for the single SNPs and SNP haplotypes that were significant in the TDT analysis ( $p < 0.05$ ) using the asthma phenotype in the combined population. These values, as well as  $\gamma$ , the relative risk (RR), and its 95% confidence interval are shown below in Table 30.

It is noted that for Table 30, the haplotypes are written without slashes separating each allele. Thus, the haplotype that is G/T/G/C/C is written as GTGCC in Table 30. This represents the short-hand designations for the haplotypes and is not, in any way, meant to represent contiguous nucleotide sequences.

**TABLE 30**

Asthma Yes/No Combined					
SNP(s)	Over-Transmitted Allele or Haplo	RR	95% Confidence Interval		Attributable Fraction
			Lower	Upper	
S1	G	1.41	0.98	2.10	47%
S2	G	1.19	0.94	1.53	24%
L-1/S1	GG	1.29	0.98	1.70	41%
L-1/S2	GG	1.27	0.99	1.63	39%
L-1/V-1	GC	1.26	0.98	1.64	39%
S1/S2	GG	1.28	1.00	1.65	40%
S1/T1	GT	1.32	1.02	1.72	42%
S2/ST+4	GA	1.08	0.88	1.33	25%
S2/ST+7	GG	1.26	1.00	1.58	37%
S2/T1	GT	1.30	1.02	1.68	41%
S2/V-4	GC	1.15	0.94	1.41	29%
S2/V-3	GG	1.08	0.88	1.33	25%
S2/V-1	GC	1.32	1.03	1.70	41%
S2/V1	GA	1.30	1.02	1.68	40%
S2/V4	GC	1.23	0.99	1.55	35%
ST+7/T1	GT	1.24	0.98	1.57	36%
T1/V-1	TC	1.25	0.98	1.61	38%
T1/V4	TC	1.21	0.97	1.51	34%
L-1/S1/S2	GGG	1.28	0.99	1.67	40%
L-1/S1/T1	GGT	1.28	0.97	1.69	41%
L-1/S1/V-4	GGC	1.13	0.91	1.42	29%
L-1/S1/V-1	GGC	1.30	1.00	1.70	41%
L-1/S1/V1	GGA	1.27	0.98	1.66	40%
L-1/S2/ST+4	GGA	1.08	0.87	1.34	25%
L-1/S2/ST+7	GGG	1.27	1.01	1.61	38%
L-1/S2/T1	GGT	1.32	1.02	1.72	42%
L-1/S2/V-4	GGC	1.14	0.93	1.42	29%
L-1/S2/V-3	GGG	1.07	0.86	1.32	24%
L-1/S2/V-1	GGC	1.32	1.03	1.72	42%
L-1/S2/V1	GGA	1.32	1.03	1.72	42%
L-1/S2/V4	GGC	1.23	0.98	1.55	35%
L-1/ST+7/T1	GGT	1.24	0.97	1.59	37%
L-1/ST+7/V-1	GGC	1.21	0.96	1.55	35%
L-1/T1/V-4	GTC	1.09	0.87	1.37	27%
L-1/T1/V-1	GTC	1.30	1.00	1.70	41%
L-1/T1/V4	GTC	1.20	0.96	1.51	34%
L-1/V-4/V-1	GCC	1.15	0.93	1.43	30%
L-1/V-3/V-1	GGC	1.05	0.85	1.30	23%
L-1/V-1/V1	GCA	1.25	0.97	1.64	39%
S1/S2/ST+4	GGA	1.06	0.86	1.32	24%
S1/S2/ST+7	GGG	1.28	1.02	1.63	39%
S1/S2/T1	GGT	1.28	1.00	1.65	39%
S1/S2/V-4	GGC	1.17	0.94	1.45	31%

S1/S2/V-3	GGG	1.06	0.86	1.32	24%
S1/S2/V-1	GGC	1.29	1.01	1.67	40%
S1/S2/V1	GGA	1.28	1.00	1.66	40%
S1/S2/V4	GGC	1.22	0.98	1.53	35%
S1/ST+4/T1	GAT	1.08	0.88	1.34	25%
S1/ST+7/T1	GGT	1.30	1.02	1.66	40%
S1/T1/V-4	GTC	1.21	0.98	1.50	33%
S1/T1/V-3	GTG	1.10	0.89	1.37	27%
S1/T1/V-1	GTC	1.30	1.01	1.69	41%
S1/T1/V1	GTA	1.28	1.00	1.66	40%
S1/T1/V4	GTC	1.21	0.97	1.51	34%
S2/ST+4/T1	GAT	1.11	0.90	1.38	28%
S2/ST+4/V-4	GAC	1.11	0.90	1.38	27%
S2/ST+4/V-3	GAG	1.11	0.89	1.39	28%
S2/ST+4/V-1	GAC	1.10	0.89	1.36	27%
S2/ST+4/V1	GAA	1.08	0.87	1.34	25%
S2/ST+4/V4	GAC	1.08	0.87	1.34	26%
S2/ST+7/T1	GGT	1.33	1.05	1.69	41%
S2/ST+7/V-4	GGC	1.08	0.88	1.33	25%
S2/ST+7/V-3	GGG	1.06	0.86	1.31	23%
S2/ST+7/V-1	GGC	1.32	1.05	1.67	40%
S2/ST+7/V1	GGA	1.30	1.04	1.65	40%
S2/ST+7/V4	GGC	1.25	1.01	1.56	36%
S2/T1/V-4	GTC	1.23	0.99	1.53	35%
S2/T1/V-3	GTG	1.12	0.90	1.40	28%
S2/T1/V-1	GTC	1.31	1.03	1.70	41%
S2/T1/V1	GTA	1.31	1.02	1.69	41%
S2/T1/V4	GTC	1.24	1.00	1.56	36%
S2/V-4/V-3	GCG	1.04	0.84	1.29	23%
S2/V-4/V-1	GCC	1.20	0.97	1.49	33%
S2/V-4/V1	GCA	1.20	0.97	1.49	33%
S2/V-4/V4	GCC	1.17	0.94	1.46	31%
S2/V-3/V-1	GGC	1.10	0.89	1.36	27%
S2/V-3/V1	GGA	1.08	0.87	1.34	25%
S2/V-3/V4	GGC	1.12	0.90	1.40	29%
S2/V-1/V1	GCA	1.31	1.03	1.69	41%
S2/V-1/V4	GCC	1.21	0.97	1.51	34%
S2/V1/V4	GAC	1.22	0.98	1.53	35%
ST+4/ST+7/T1	AGT	1.04	0.84	1.29	22%
ST+4/T1/V-1	ATC	1.12	0.91	1.38	28%
ST+4/T1/V4	ATC	1.10	0.89	1.36	26%
ST+7/T1/V-4	GTC	1.13	0.92	1.40	29%
ST+7/T1/V-3	GTG	1.05	0.85	1.31	24%
ST+7/T1/V-1	GTC	1.25	0.99	1.59	37%
ST+7/T1/V1	GTA	1.23	0.97	1.57	36%
ST+7/T1/V4	GTC	1.22	0.98	1.52	34%
ST+7/V-4/V-1	GCC	1.05	0.84	1.31	24%
T1/V-4/V-1	TCC	1.23	1.00	1.52	34%
T1/V-4/V4	TCC	1.19	0.96	1.48	32%



T1/V-3/V-1	TGC	1.13	0.92	1.40	29%
T1/V-3/V4	TGC	1.13	0.92	1.40	29%
T1/V-1/V1	TCA	1.25	0.97	1.61	38%
T1/V-1/V4	TCC	1.21	0.97	1.51	34%
T1/V1/V4	TAC	1.23	1.00	1.54	35%
S1/T1/V-1/V1	GTCA	1.29	1.00	1.67	40%
S1/T1/V-1/V4	GTCC	1.23	0.99	1.54	35%
S1/T1/V1/V4	GTAC	1.23	0.99	1.54	35%
S2/ST+7/T1/V-4	GGTC	1.16	0.93	1.45	31%
S2/ST+7/T1/V-3	GGTG	1.08	0.87	1.35	26%
S2/ST+7/T1/V-1	GGTC	1.34	1.06	1.70	41%
S2/ST+7/T1/V4	GGTC	1.27	1.02	1.59	37%
S2/ST+7/V-4/V-1	GGCC	1.14	0.92	1.42	29%
S2/ST+7/V-4/V4	GGCC	1.12	0.89	1.40	28%
S2/ST+7/V-3/V-1	GGGC	1.06	0.85	1.31	24%
S2/ST+7/V-3/V4	GGGC	1.07	0.85	1.33	25%
S2/ST+7/V-1/V4	GGCC	1.24	1.00	1.55	35%
S2/T1/V-4/V-1	GTCC	1.24	1.00	1.54	35%
S2/T1/V-4/V4	GTCC	1.21	0.97	1.52	34%
S2/T1/V-3/V-1	GTGC	1.14	0.92	1.42	30%
S2/T1/V-3/V4	GTGC	1.17	0.94	1.47	32%
S2/T1/V-1/V4	GTCC	1.22	0.97	1.53	35%
S2/V-4/V-1/V4	GCCC	1.15	0.92	1.43	30%
S2/V-3/V-1/V4	GGCC	1.12	0.90	1.39	28%
ST+7/T1/V-4/V-1	GTCC	1.16	0.94	1.44	30%
ST+7/T1/V-4/V4	GTCC	1.15	0.92	1.44	30%
ST+7/T1/V-3/V-1	GTGC	1.08	0.87	1.34	25%
ST+7/T1/V-3/V4	GTGC	1.09	0.88	1.36	27%
ST+7/T1/V-1/V4	GTCC	1.21	0.98	1.51	34%
T1/V-4/V-1/V4	TCCC	1.19	0.96	1.49	33%
T1/V-3/V-1/V4	TGCC	1.16	0.94	1.45	31%
T1/V-1/V1/V4	TCAC	1.20	0.96	1.50	33%
S1/T1/V-1/V1/V4	GTCA	1.22	0.98	1.52	34%
S2/ST+7/T1/V-3/V-1	GTGCC	1.09	0.88	1.36	27%
S2/ST+7/T1/V-3/V4	GGTGC	1.10	0.88	1.38	28%
S2/ST+7/T1/V-1/V4	GGTCC	1.26	1.01	1.58	37%
S2/ST+7/V-3/V-1/V4	GGTGC	1.07	0.85	1.33	25%
S2/T1/V-3/V-1/V4	GTGCC	1.17	0.93	1.46	31%
ST+7/T1/V-3/V-1/V4	GTGCC	1.09	0.88	1.36	27%

The alleles that conferred increased risk of developing asthma appeared common. Haplotype frequencies ranged from 31% to 89%. This effect translated into a substantial population attributable risk, with estimates ranging from 2 to 47% for different SNPs or SNP haplotypes. These computations

5 depended heavily on allele frequency and risk estimates.

Conclusion: Gene 216 has been demonstrated to be an asthma gene in accordance with the data disclosed herein, including: 1) localization to a region on chromosome 20 identified through linkage; 2) polymorphism analysis performed to identify sequence variants localized in the candidate gene; 3) 5 genotype analyses of the identified polymorphisms; 4) association between identified alleles and the asthma phenotype in a case-control analysis; 5) association between identified alleles and the asthma phenotype in transmission disequilibrium tests (TDT), haplotype analyses, and analyses using additional phenotypes; 6) identification of transcripts in tissues relevant 10 to pulmonary disease and/or inflammation; and 7) characterization of Gene 216 as an ADAM family member. It is noted that Gene 216 is also likely to be involved in obesity and inflammatory bowel disease, as obesity (Wilson et al., 1999, *Arch. Intern. Med.* **159**: 2513-14) and inflammatory bowel disease (B. Wallaert et al., 1995, *J. Exp. Med.* **182**:1897-1904) have been linked to 15 asthma.

The disclosure of each of the patents, patent applications, and publications cited in the specification is hereby incorporated by reference herein in its entirety.

20

Although the invention has been set forth in detail, one skilled in the art will recognize that numerous changes and modifications can be made, and that such changes and modifications may be made without departing from the spirit and scope of the invention.

25

**WHAT IS CLAIMED IS:**

1. An isolated nucleic acid which comprises SEQ ID NO:6, and contains at least one allele selected from the group consisting of:
  - a. allele G at single nucleotide polymorphism F+1;
  - b. allele A at single nucleotide polymorphism L-1;
  - c. allele G at single nucleotide polymorphism L-1;
  - d. allele T at single nucleotide polymorphism M+1;
  - e. allele C at single nucleotide polymorphism Q-1;
  - f. allele G at single nucleotide polymorphism ST+7;
  - g. allele A at single nucleotide polymorphism ST+4;
  - h. allele T at single nucleotide polymorphism T+1; and
  - i. allele C at single nucleotide polymorphism V-1.
  
2. An isolated nucleic acid which comprises SEQ ID NO:6, and contains at least one allele selected from the group consisting of:
  - a. allele A at single nucleotide polymorphism I1;
  - b. allele G at single nucleotide polymorphism S1;
  - c. allele G at single nucleotide polymorphism S2;
  - d. allele C at single nucleotide polymorphism S2;
  - e. allele C at single nucleotide polymorphism T1;
  - f. allele T at single nucleotide polymorphism T2;
  - g. allele C at single nucleotide polymorphism V4; and
  - h. allele G for single nucleotide polymorphism V7.
  
3. An isolated nucleic acid which comprises at least 50 consecutive nucleotides of SEQ ID NO:6, and contains at least one allele selected from the group consisting of:
  - a. allele G at single nucleotide polymorphism F+1;
  - b. allele A at single nucleotide polymorphism L-1;
  - c. allele T at single nucleotide polymorphism M+1;
  - d. allele C at single nucleotide polymorphism Q-1;

- e. allele G at single nucleotide polymorphism ST+7;
  - f. allele A at single nucleotide polymorphism ST+4;
  - g. allele T at single nucleotide polymorphism T+1; and
  - h. allele C at single nucleotide polymorphism V-1.
4. An isolated nucleic acid which comprises at least 50 consecutive nucleotides of SEQ ID NO:6, and contains at least one allele selected from the group consisting of:
- a. allele A at single nucleotide polymorphism I1;
  - b. allele G at single nucleotide polymorphism S1;
  - c. allele G at single nucleotide polymorphism S2;
  - d. allele C at single nucleotide polymorphism S2;
  - e. allele C at single nucleotide polymorphism T1;
  - f. allele T at single nucleotide polymorphism T2;
  - g. allele C at single nucleotide polymorphism V4; and
  - h. allele G for single nucleotide polymorphism V7.
5. An isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6, and contains at least one allele selected from the group consisting of:
- a. allele G at single nucleotide polymorphism F+1;
  - b. allele A at single nucleotide polymorphism L-1;
  - c. allele T at single nucleotide polymorphism M+1;
  - d. allele C at single nucleotide polymorphism Q-1;
  - e. allele G at single nucleotide polymorphism ST+7;
  - f. allele A at single nucleotide polymorphism ST+4;
  - g. allele T at single nucleotide polymorphism T+1; and
  - h. allele C at single nucleotide polymorphism V-1.
6. An isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6, and contains at least one allele selected from

the group consisting of:

- a. allele A at single nucleotide polymorphism I1;
- b. allele G at single nucleotide polymorphism S1;
- c. allele G at single nucleotide polymorphism S2;
- d. allele C at single nucleotide polymorphism S2;
- e. allele C at single nucleotide polymorphism T1;
- f. allele T at single nucleotide polymorphism T2;
- g. allele C at single nucleotide polymorphism V4; and
- h. allele G for single nucleotide polymorphism V7.

7. An isolated nucleic acid which comprises at least 1520 consecutive nucleotides of SEQ ID NO:6, and contains at least one haplotype selected from the group consisting of:
  - a. haplotype C/G at single nucleotide polymorphisms ST+4/V-3;
  - b. haplotype C/C at single nucleotide polymorphisms ST+4/V-2;
  - c. haplotype C/C at single nucleotide polymorphisms ST+4/V-4;
  - d. haplotype A/C at single nucleotide polymorphisms ST+7/V-2;
  - e. haplotype T/C at single nucleotide polymorphisms S+1/ST+4; and
  - f. haplotype C/T at single nucleotide polymorphism ST+4/ST+5.
8. An isolated nucleic acid which comprises at least 2070 consecutive nucleotides of SEQ ID NO:6, and contains at least one haplotype selected from the group consisting of:
  - a. haplotype C/T at single nucleotide polymorphisms S2/T+2; and
  - b. haplotype G/C at single nucleotide polymorphisms S2/V-1.
9. An isolated nucleic acid which comprises at least 3915 consecutive nucleotides of SEQ ID NO:6, and contains at least one haplotype selected from the group consisting of:
  - a. haplotype G/A at single nucleotide polymorphisms F+1/ST+4;
  - b. haplotype C/A at single nucleotide polymorphisms KL+2/ST+4;

- c. haplotype G/A at single nucleotide polymorphisms L-1/ST+7;
  - d. haplotype G/C at single nucleotide polymorphisms L-1/V-1;
  - e. haplotype T/G at single nucleotide polymorphisms Q-1/T+2;
  - f. haplotype C/A at single nucleotide polymorphisms Q-1/ST+4;
  - g. haplotype A/G at single nucleotide polymorphisms ST+4/ST+7;
  - h. haplotype A/C at single nucleotide polymorphisms ST+4/V-1; and
  - i. haplotype G/A at single nucleotide polymorphisms T+2/V-1.
10. An isolated nucleic acid which comprises at least 5009 consecutive nucleotides of SEQ ID NO:6, and contains at least one haplotype selected from the group consisting of:
- a. haplotype A/A at single nucleotide polymorphisms I1/ST+4;
  - b. haplotype A/A at single nucleotide polymorphism I1/V1;
  - c. haplotype A/C at single nucleotide polymorphisms I1/V2;
  - d. haplotype A/T at single nucleotide polymorphisms I1/V3;
  - e. haplotype A/A at single nucleotide polymorphisms S1/S+1;
  - f. haplotype G/A at single nucleotide polymorphisms S1/ST+4;
  - g. haplotype G/T at single nucleotide polymorphisms S1/T1
  - h. haplotype G/A at single nucleotide polymorphisms S2/ST+4;
  - i. haplotype G/C at single nucleotide polymorphisms S2/V-1;
  - j. haplotype A/C at single nucleotide polymorphisms ST+4/V4;
  - k. haplotype C/C at single nucleotide polymorphisms S2/V6;
  - l. haplotype A/C at single nucleotide polymorphisms ST+4/V7;
  - m. haplotype G/T at single nucleotide polymorphisms ST+7/T1;
  - n. haplotype T/C at single nucleotide polymorphisms T1/V4;
  - o. haplotype C/C at single nucleotide polymorphisms V-1/V4;
  - p. haplotype G/G/T at single nucleotide polymorphisms S2/ST+7/T1
  - q. haplotype G/G/C at single nucleotide polymorphisms S2/ST+7/V-1;
  - r. haplotype G/T/C at single nucleotide polymorphisms ST+7/T1/V4;
  - s. haplotype G/G/T/C at single nucleotide polymorphisms

S2/ST+7/T1/V-1;

t. haplotype G/G/T/G/C at single nucleotide polymorphisms S2/ST+7/T1/V-3/V-1; and

u. haplotype G/G/T/C/C at single nucleotide polymorphisms S2/ST+7/T1/V-1/V4.

11. An isolated nucleic acid which comprises at least 6875 consecutive nucleotides of SEQ ID NO:6, and contains at least one haplotype selected from the group consisting of:

a. haplotype T/A/A/C/G/C/T/C/A/C/C/G/A/C/C at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

b. haplotype T/A/A/C/G/C/C/C/A/C/T/C/A/C/G at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

c. haplotype T/A/A/C/G/C/C/T/A/C/T/C/A/C/G at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

d. haplotype T/A/A/C/G/C/C/T/A/C/T/C/A/T/G at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

e. haplotype T/A/G/C/A/C/T/C/A/C/T/G/A/C/G at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

f. T/A/G/C/A/C/T/C/A/C/T/G/A/C/G alleles at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

g. haplotype T/A/G/C/G/G/T/C/A/C/T/G/A/T/G at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

h. haplotype T/A/G/C/G/G/T/C/A/C/T/G/A/C/C at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

i. haplotype T/A/G/C/G/G/T/C/A/C/T/C/A/C/C at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

j. haplotype T/A/G/C/G/G/T/C/A/C/T/C/A/C/C at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

k. haplotype T/A/G/C/G/G/T/C/A/C/T/C/A/C/G at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7;

- l. haplotype T/A/G/C/G/G/T/C/A/C/T/C/A/C/G at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7; and
- m. haplotype T/G/A/C/G/C/T/C/T/T/C/G/G/C/G at single nucleotide polymorphisms D1/F1/I1/L1/S1/S2/T1/T2/V1/V2/V3/V4/V5/V6/V7.

12. A set of isolated nucleic acids comprising:

- a. a first isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele C at single nucleotide polymorphism ST+4; and
- b. a second isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:
  - 1. allele G at single nucleotide polymorphism V-3;
  - 2. allele C at single nucleotide polymorphism V-2;
  - 3. allele C at single nucleotide polymorphism V-4;
  - 4. allele T at single nucleotide polymorphism S+1; and
  - 5. allele T at single nucleotide polymorphism ST+5.

13. A set of isolated nucleic acids comprising:

- a. a first isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele C at single nucleotide polymorphism S2; and
- b. a second isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:
  - 1. allele C at single nucleotide polymorphism V6; and
  - 2. allele T at single nucleotide polymorphism T+2.

14. A set of isolated nucleic acids comprising:

- a. a first isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele A at single



nucleotide polymorphism ST+7; and

b. a second isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele C at single nucleotide polymorphism V-2.

15. A set of isolated nucleic acids comprising:

a. a first isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele A at single nucleotide polymorphism ST+4; and

b. a second isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele C at single nucleotide polymorphism Q+1;
2. allele C at single nucleotide polymorphism KL+2;
3. allele G at single nucleotide polymorphism ST+7;
4. allele C at single nucleotide polymorphism V-1;
5. allele C at single nucleotide polymorphism V4;
6. allele G at single nucleotide polymorphism F+1
7. allele G at single nucleotide polymorphism S1;
8. allele G at single nucleotide polymorphism S2;
9. allele C at single nucleotide polymorphism V7; and
10. allele A at single nucleotide polymorphism I1.

16. A set of isolated nucleic acids comprising:

a. a first isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele A at single nucleotide polymorphism I1; and

b. a second isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele A at single nucleotide polymorphism ST+4;

2. allele T at single nucleotide polymorphism V3;
3. allele C at single nucleotide polymorphism V2; and
4. allele A at single nucleotide polymorphism V1.

17. A set of isolated nucleic acids comprising:

a. a first isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele G at single nucleotide polymorphism T+2; and

b. a second isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele T at single nucleotide polymorphism Q-1; and
2. allele A at single nucleotide polymorphism V-1.

18. A set of isolated nucleic acids comprising:

a. a first isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele C at single nucleotide polymorphism V-1; and

b. a second isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele C at single nucleotide polymorphism V4;
2. allele G at single nucleotide polymorphism L-1; and
3. allele G at single nucleotide polymorphism T+2.

19. A set of isolated nucleic acids comprising:

a. a first isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele A at single nucleotide polymorphism S1; and

b. a second isolated nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele C at single

nucleotide polymorphism S+1.

20. A set of isolated nucleic acids comprising:
  - a. a first isolated nucleic acid which is complementary to the first isolated nucleic acid of any one of claims 12-19; and
  - b. a second isolated nucleic acid which is complementary to the second isolated nucleic acid of any one of claims 12-19.
21. A isolated nucleic acid which is complementary to the nucleic acid of any one of claims 5-6.
22. An isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NO:242-284 and SEQ ID NO:373-420.
23. An isolated nucleic acid which is complementary to the nucleic acid of claim 22.
24. An isolated nucleic acid comprising at least 15 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NO:242-284 and SEQ ID NO:373-420, wherein the sequence contains at least one allele shown in Table 10.
25. An isolated nucleic acid which is complementary to the nucleic acid of claim 24.
26. A probe comprising the isolated nucleic acid of claim 24.
27. A probe comprising the isolated nucleic acid of claim 25.
28. A primer comprising the isolated nucleic acid of claim 24.
29. A primer comprising the isolated nucleic acid of claim 25.
30. An isolated amino acid sequence encoded by the isolated nucleic acid of any one of claims 2, 4, 6, 10, and 11.
31. An isolated amino acid sequence encoded by the isolated nucleic acid

of claim 8.

32. An antibody which binds to the isolated amino acid sequence of claim 30, wherein antibody is polyclonal or monoclonal.
33. An antibody which binds to the isolated amino acid sequence of claim 31, wherein antibody is polyclonal or monoclonal.
34. An antibody fragment of the antibody of claim 32, wherein the antibody fragment binds to the isolated amino acid sequence.
35. An antibody fragment of the antibody of claim 33, wherein the antibody fragment binds to the isolated amino acid sequence.
36. A vector comprising the isolated nucleic acid of any one of claims 2, 4, 6, 8, 10, and 11.
37. A vector comprising the isolated nucleic acid of any one of claims 1, 3, 5, 7, and 9.
38. A vector comprising the isolated nucleic acid of claim 21.
39. A vector comprising the isolated nucleic acid of claim 24.
40. A kit for detecting a Gene 216 nucleic acid molecule comprising:
  - a. the isolated nucleic acid of any one of claims 5-6; and
  - b. at least one component to detect hybridization of the isolated nucleic acid to the Gene 216 nucleic acid molecule.
41. A kit for detecting a Gene 216 nucleic acid molecule comprising:
  - a. the isolated nucleic acid of claim 21 and
  - b. at least one component to detect hybridization of the isolated nucleic acid to the Gene 216 nucleic acid molecule.
42. A kit for detecting a Gene 216 nucleic acid molecule comprising:
  - a. the probe of any one of claims 24-25; and
  - b. at least one component to detect hybridization of the probe to the

Gene 216 nucleic acid molecule.

43. A kit for detecting a Gene 216 nucleic acid molecule comprising:
  - a. the set of isolated nucleic acids of any one of claims 12-20; and
  - b. at least one component to detect hybridization of one or more of the nucleic acids of the set to a Gene 216 nucleic acid molecule.
44. A kit for detecting a Gene 216 amino acid sequence comprising:
  - a. the antibody of claim 32; and
  - b. at least one component to detect binding of the antibody to a Gene 216 amino acid sequence.
45. A kit for detecting a Gene 216 amino acid sequence comprising:
  - a. the antibody of claim 33; and
  - b. at least one component to detect binding of the antibody to a Gene 216 amino acid sequence.
46. A kit for detecting a Gene 216 amino acid sequence comprising:
  - a. the antibody fragment of claim 34; and
  - b. at least one component to detect binding of the antibody fragment to a Gene 216 amino acid sequence.
47. A kit for detecting a Gene 216 amino acid sequence comprising:
  - a. the antibody fragment of claim 35; and
  - b. at least one component to detect binding of the antibody fragment to a Gene 216 amino acid sequence.
48. A pharmaceutical composition comprising the isolated nucleic acid of claim 21, and a physiologically acceptable carrier, excipient, or diluent.
49. A pharmaceutical composition comprising the isolated nucleic acid of claim 25, and a physiologically acceptable carrier, excipient, or diluent.
50. A pharmaceutical composition comprising the antibody of claim 32, and a physiologically acceptable carrier, excipient, or diluent.
51. A pharmaceutical composition comprising the antibody fragment of

- claim 34, and a physiologically acceptable carrier, excipient, or diluent.
52. A pharmaceutical composition comprising the vector of claim 38, and a physiologically acceptable carrier, excipient, or diluent.
53. A pharmaceutical composition comprising the vector of claim 39, and a physiologically acceptable carrier, excipient, or diluent.
54. A method of treating a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness comprising: administering the pharmaceutical composition of claim 48 in an amount effective to treat the disorder.
55. A method of treating a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness comprising: administering the pharmaceutical composition of claim 49 in an amount effective to treat the disorder.
56. A method of treating a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness comprising: administering the pharmaceutical composition of claim 50 in an amount effective to treat the disorder.
57. A method of treating a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness comprising: administering the pharmaceutical composition of claim 51 in an amount effective to treat the disorder.
58. A method of treating a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness comprising: administering the pharmaceutical composition of claim 52 in an amount effective to treat the disorder.
59. A method of treating a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness comprising: administering the pharmaceutical composition of claim 53 in an amount effective to treat the

disorder.

60. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises at least 15 consecutive nucleotides of SEQ ID NO:6, and contains at least one allele selected from the group consisting of:

- a. allele G at single nucleotide polymorphism F+1;
- b. allele A at single nucleotide polymorphism L-1;
- c. allele G at single nucleotide polymorphism L-1;
- d. allele T at single nucleotide polymorphism M+1;
- e. allele C at single nucleotide polymorphism Q-1;
- f. allele G at single nucleotide polymorphism ST+7;
- g. allele A at single nucleotide polymorphism ST+4;
- h. allele T at single nucleotide polymorphism T+1;
- i. allele C at single nucleotide polymorphism V-1;
- j. allele A at single nucleotide polymorphism I1;
- k. allele G at single nucleotide polymorphism S1;
- l. allele G at single nucleotide polymorphism S2;
- m. allele C at single nucleotide polymorphism S2;
- n. allele C at single nucleotide polymorphism T1;
- o. allele T at single nucleotide polymorphism T2;
- p. allele C at single nucleotide polymorphism V4; and
- q. allele G for single nucleotide polymorphism V7;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

61. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which is complementary to the nucleic

acid of claim 60, wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder

62. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises two regions, including:

a. a first region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele A at single nucleotide polymorphism ST+4; and

b. a second region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele C at single nucleotide polymorphism Q+1;
2. allele C at single nucleotide polymorphism KL+2;
3. allele G at single nucleotide polymorphism ST+7;
4. allele C at single nucleotide polymorphism V-1;
5. allele C at single nucleotide polymorphism V4;
6. allele G at single nucleotide polymorphism F+1
7. allele G at single nucleotide polymorphism S1;
8. allele G at single nucleotide polymorphism S2;
9. allele C at single nucleotide polymorphism V7; and
10. allele A at single nucleotide polymorphism I1;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

63. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises two regions, including:

a. a first region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele A at single nucleotide polymorphism I1;



and

b. a second region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele A at single nucleotide polymorphism ST+4;
2. allele T at single nucleotide polymorphism V3;
3. allele C at single nucleotide polymorphism V2; and
4. allele A at single nucleotide polymorphism V1;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

64. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises two regions, including:

a. a first region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele G at single nucleotide polymorphism T+2; and

b. a second region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele T at single nucleotide polymorphism Q-1; and
2. allele A at single nucleotide polymorphism V-1;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

65. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises two regions, including:

a. a first region which comprises at least 15 consecutive nucleotides

of SEQ ID NO:6 and contains allele C at single nucleotide polymorphism V-1;  
and

b. a second region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele C at single nucleotide polymorphism V4;
2. allele G at single nucleotide polymorphism L-1; and
3. allele G at single nucleotide polymorphism T+2;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

66. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises two regions, including:

a. a first region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele A at single nucleotide polymorphism S1;  
and

b. a second region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele C at single nucleotide polymorphism S+1;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

67. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises two regions, including:

a. a first region is complementary to the first region of any one of claims 62-66; and

b. a second region is complementary to the second region of any

one of claims 62-66;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

68. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises three regions, including:

a. a first region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele G at single nucleotide polymorphism S2; and

b. a second region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele G at single nucleotide polymorphism ST+7; and

c. a third region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele T of single nucleotide polymorphism T1; and
2. allele C of single nucleotide polymorphism V-1;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

69. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises three regions, including:

a. a first region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele G at single nucleotide polymorphism ST+7; and

b. a second region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele T at single nucleotide

polymorphism T1; and

c. a third region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele G of single nucleotide polymorphism S2; and
2. allele C of single nucleotide polymorphism V4;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

70. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises three regions, including:

- a. a first region which is complementary to the first region of any one of claims 68-69;
- b. a second region which is complementary to the second region of any one of claims 68-69; and
- c. a third region which is complementary to the third region of any one of claims 68-69;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

71. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises five regions, including:

- a. a first region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele G at single nucleotide polymorphism S2; and
- b. a second region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele G at single nucleotide

polymorphism ST+7;

c. a third region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele T at single nucleotide polymorphism T1;

d. a fourth region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains allele C at single nucleotide polymorphism V-1; and

e. a fifth region which comprises at least 15 consecutive nucleotides of SEQ ID NO:6 and contains an allele selected from the group consisting of:

1. allele C of single nucleotide polymorphism V-3; and
2. allele C of single nucleotide polymorphism V4;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

72. A method of identifying increased susceptibility to a disorder selected from the group consisting of asthma and bronchial hyperresponsiveness in a subject comprising: testing a biological sample obtained from a subject for the presence of a nucleic acid which comprises five regions, including:

a. a first region which is complementary to the first region of claim 71;

b. a second region which is complementary to the second region of claim 71;

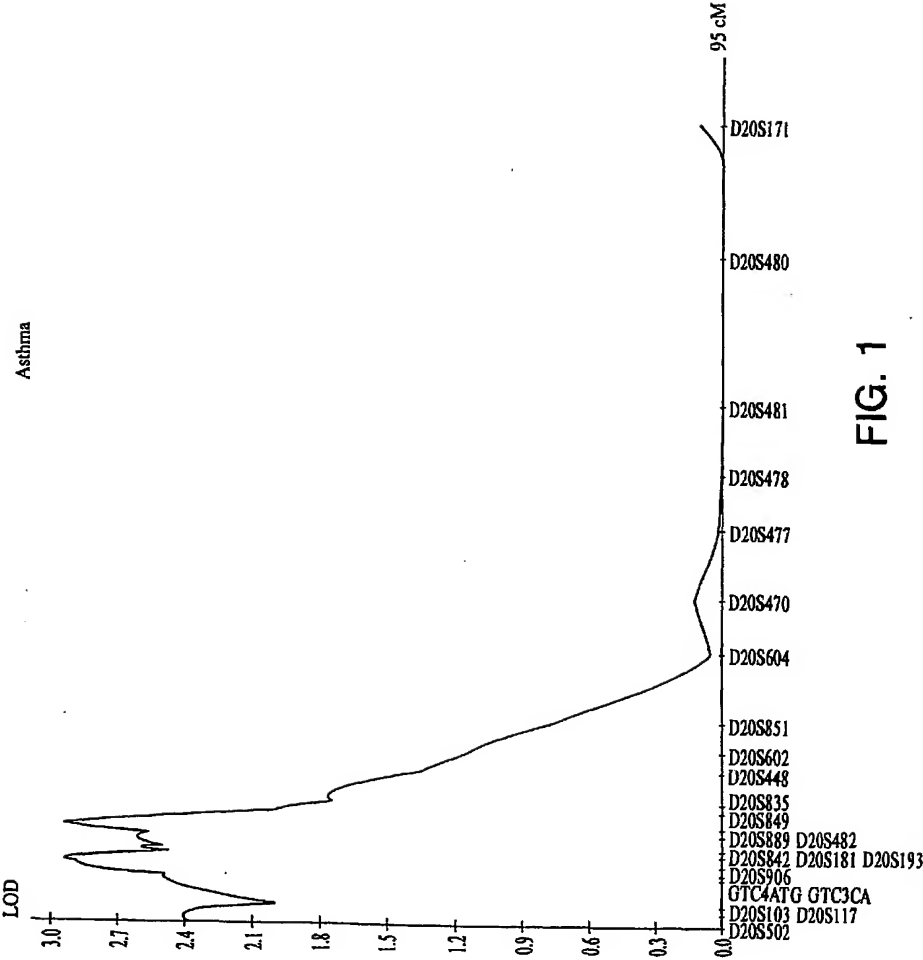
c. a third region which is complementary to the third region of claim 71;

d. a fourth region which is complementary to the fourth region of claim 71; and

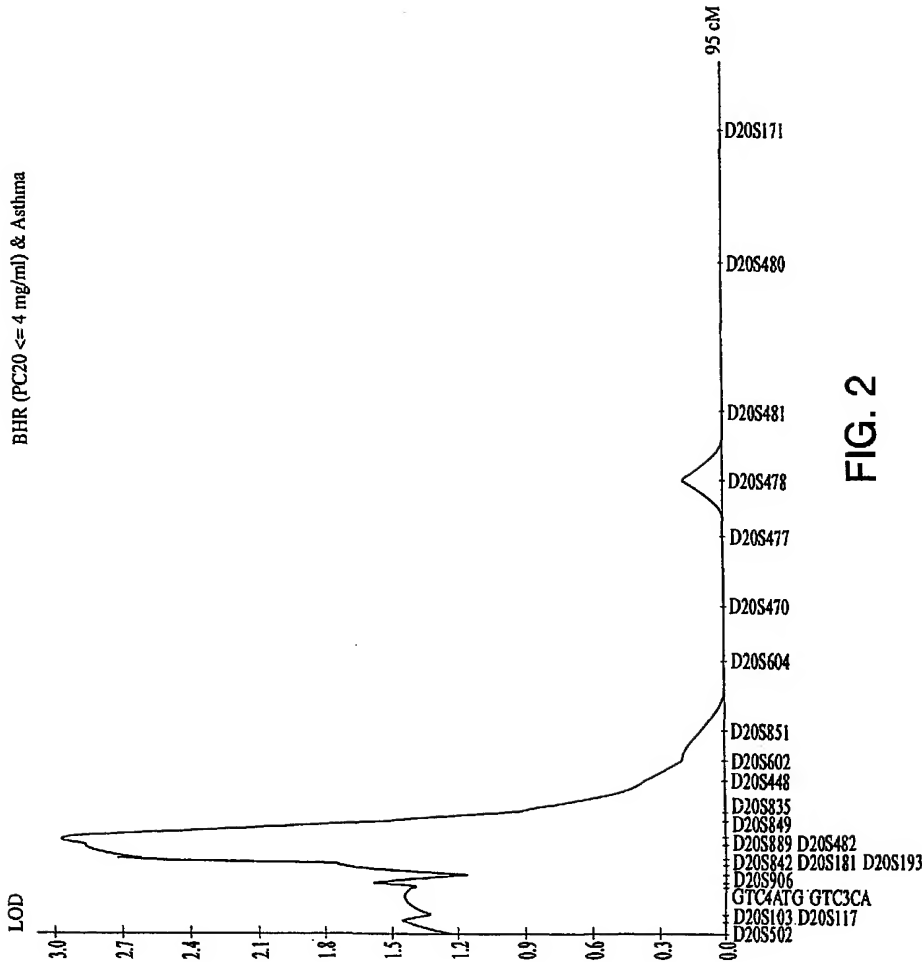
e. a fifth region which is complementary to the fifth region of claim 71;

wherein the presence of the nucleic acid identifies an increased susceptibility to the disorder.

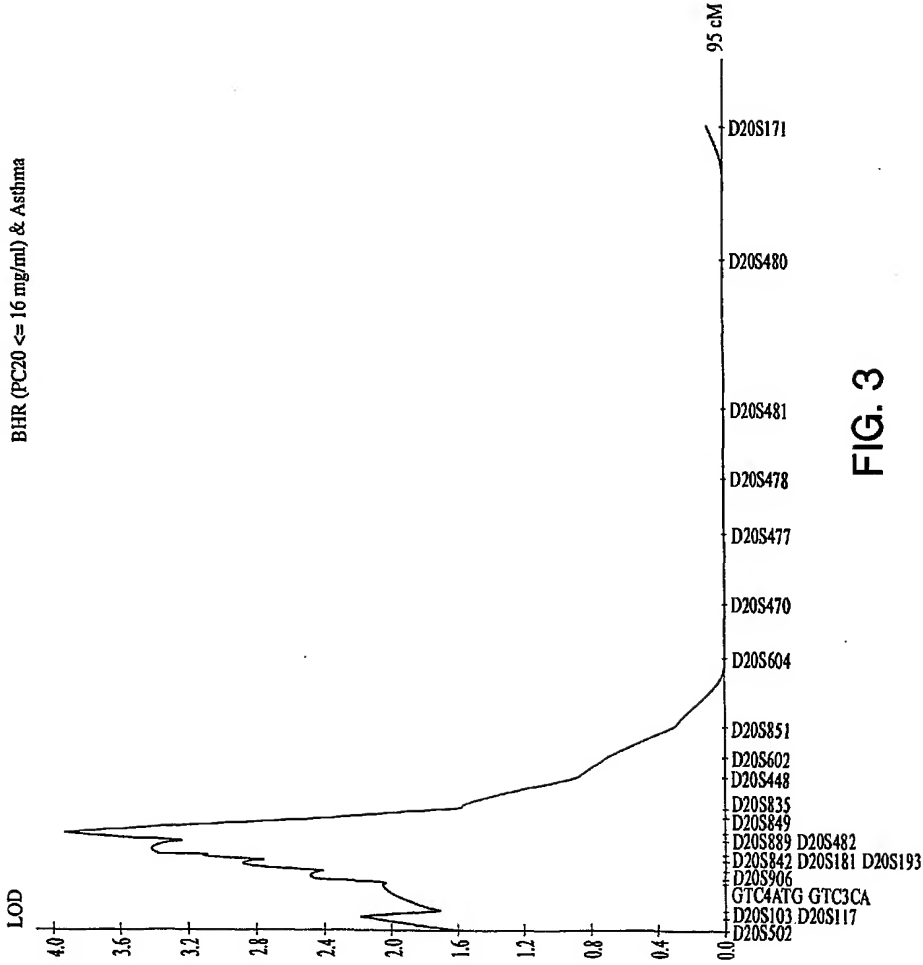
73. A biochip comprising the isolated nucleic acid of any one of claims 23 and 24.

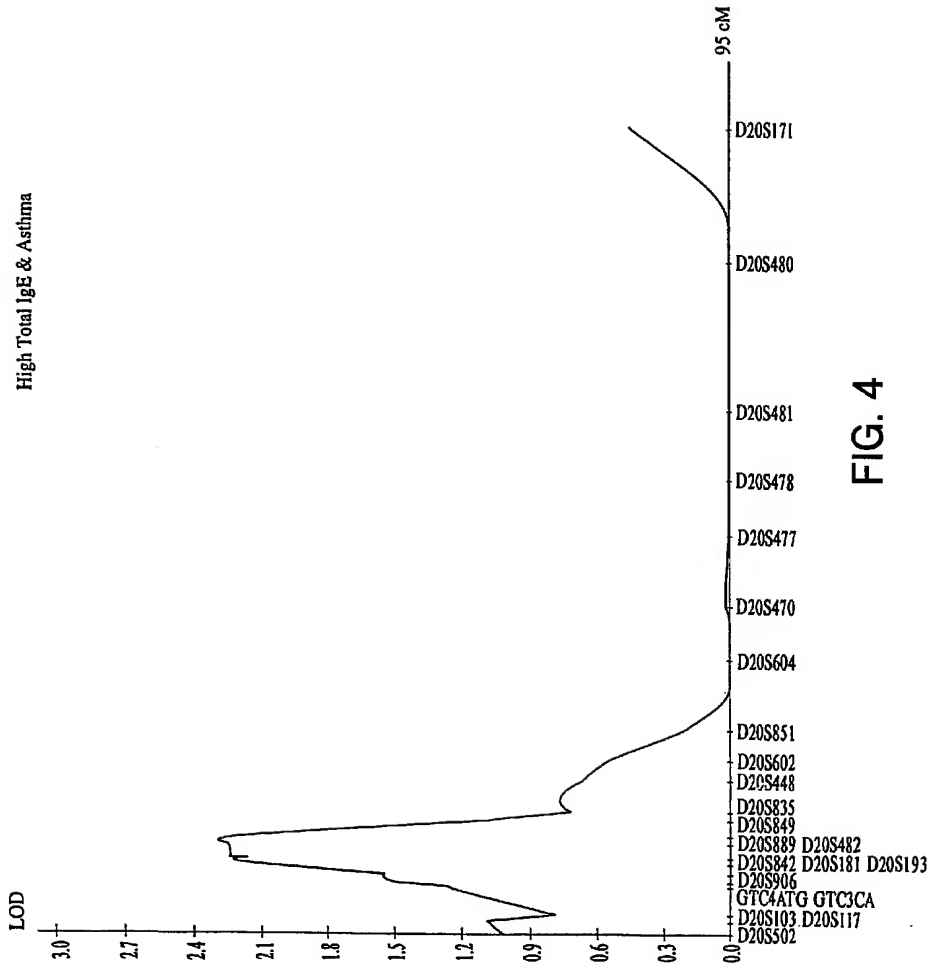


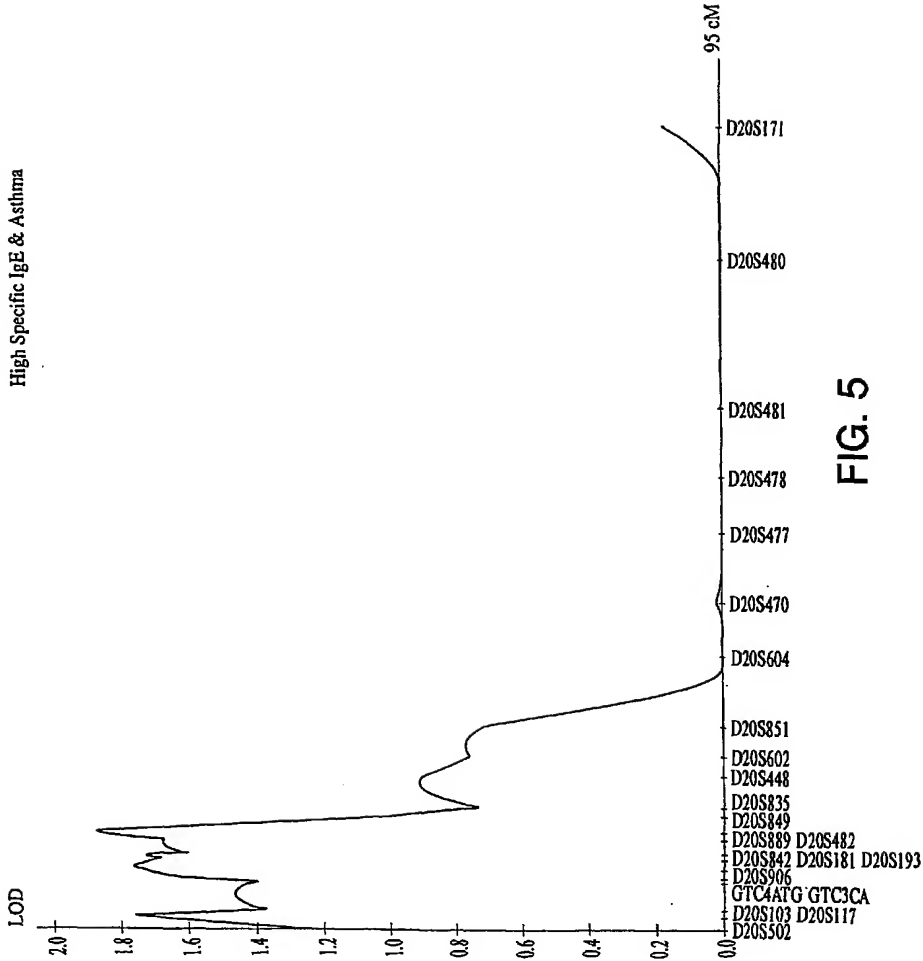
BHR (PC20 <= 4 mg/ml) & Asthma











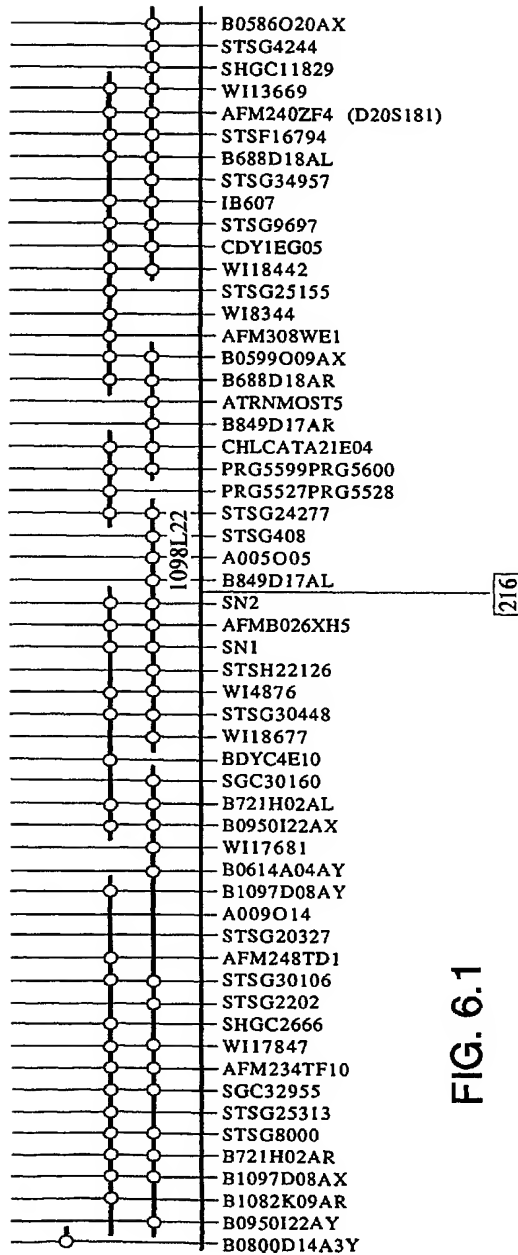


FIG. 6.1

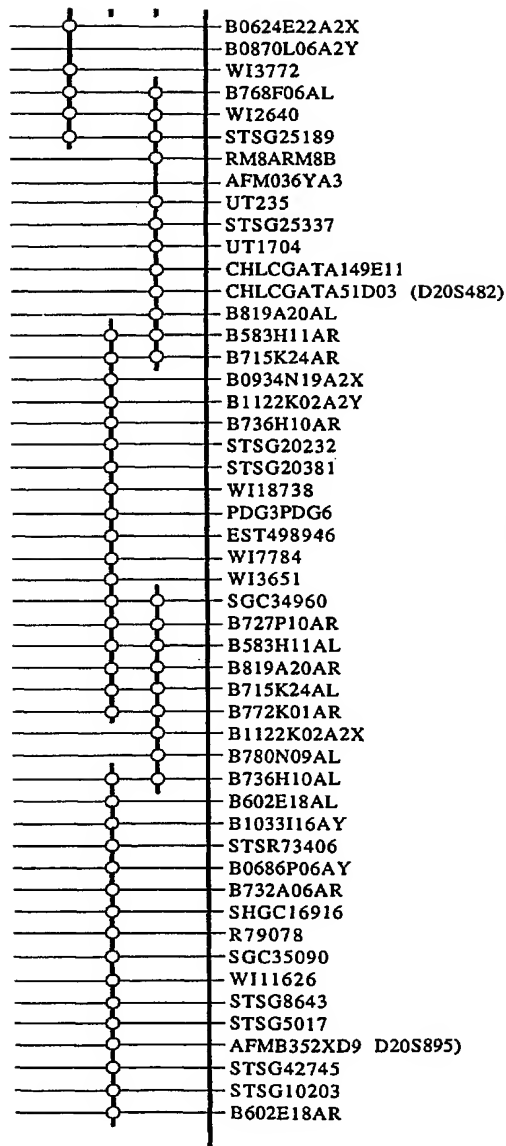


FIG. 6.2

>BAC1098L22 sequence

gctctaataaatttgcggcgctaatacgaactcactatagggagaggatccgcggaattccccatgtgccatgtccaag  
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 ccaggctggagtgagtgaggccaatttctcagctcactgcaacctccgcctccagggtcctgatctcaagcagttctctgcgc  
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FIG. 7.1

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FIG. 7.2

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FIG. 7.3



[illegible]

**FIG. 7.4**

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FIG. 7.5

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FIG. 7.6

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FIG. 7.7

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FIG. 7.8

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FIG. 7.9

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FIG. 7.10

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FIG. 7.11



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FIG. 7.12

FIG. 7.13

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FIG. 7.14

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FIG. 7.15

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FIG. 7.16

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FIG. 7.17

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FIG. 7.18

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FIG. 7.19



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FIG. 7.20

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FIG. 7.21

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FIG. 7.22

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FIG. 7.23

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**FIG. 7.24**

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FIG. 7.25

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FIG. 7.26

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FIG. 7.27



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**FIG. 7.28**

[illegible]

FIG. 7.29

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FIG. 7.30

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FIG. 7.31

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FIG. 7.32

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FIG. 7.33

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FIG. 7.34

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FIG. 7.35



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FIG. 7.36

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FIG. 7.37

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FIG. 7.38

FIG. 7.39



FIG. 7.41

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FIG. 7.42

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**FIG. 7.43**



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FIG. 7.44

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FIG. 7.45

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FIG. 7.46

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FIG. 7.47

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FIG. 7.48

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FIG. 7.49

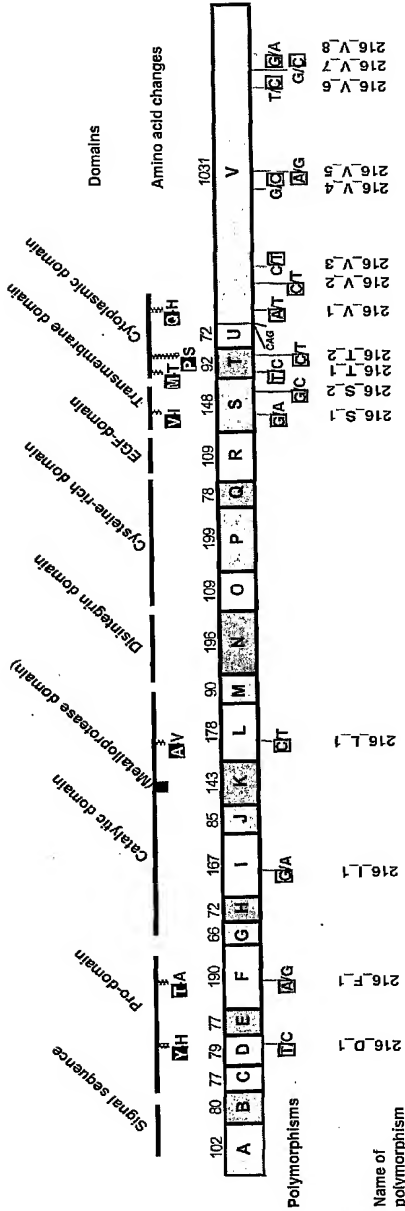


FIG. 8

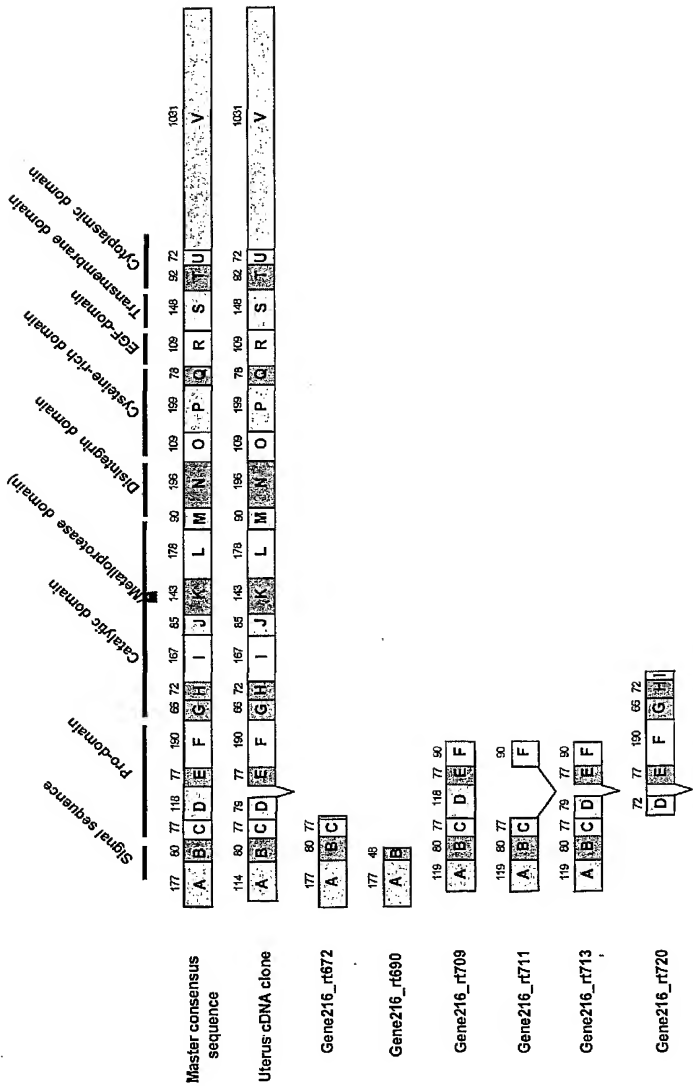


FIG. 9



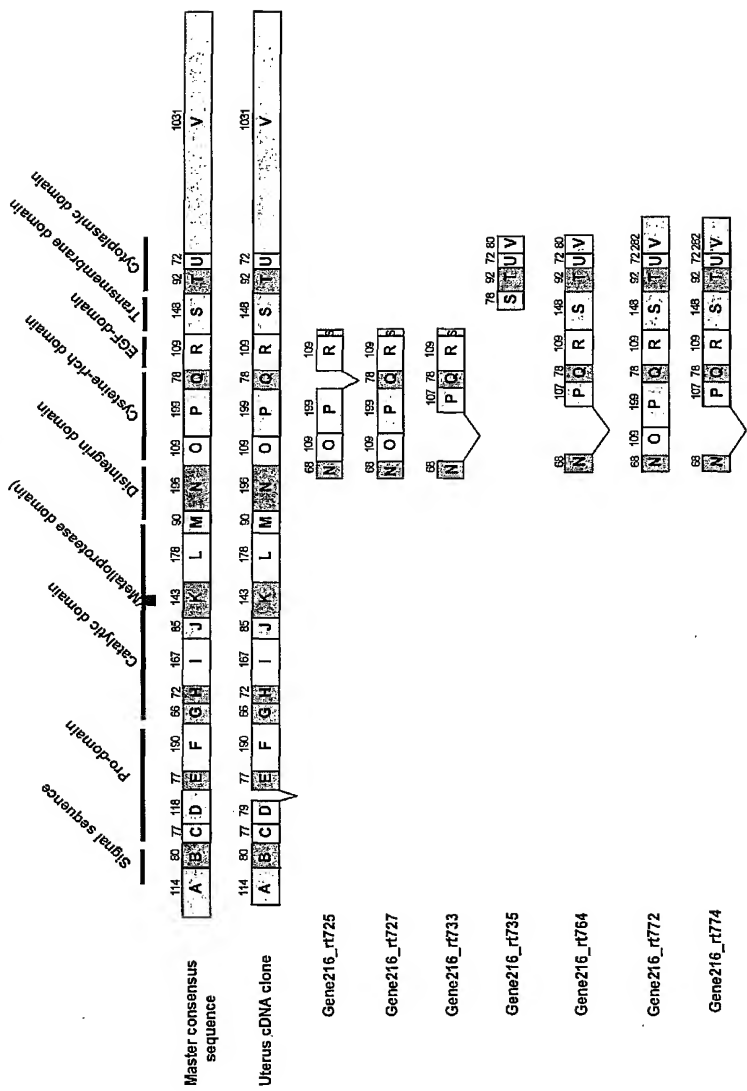


FIG. 10

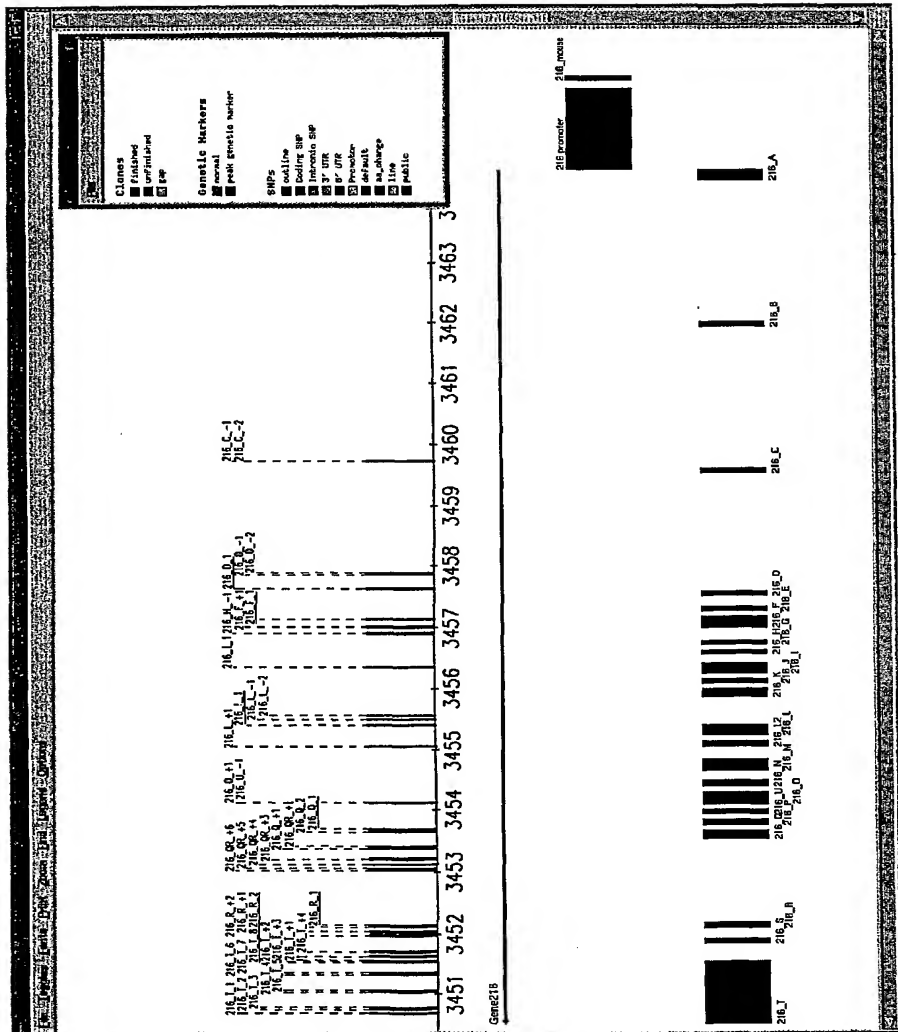


FIG. 11

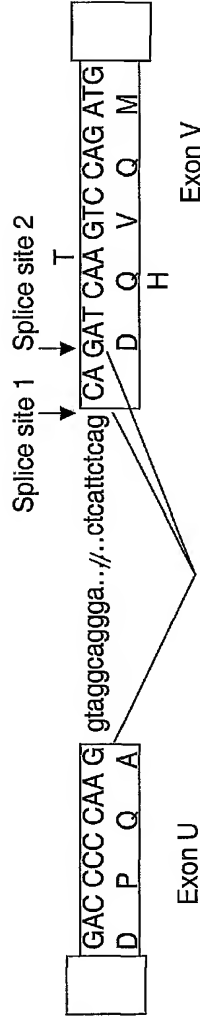


FIG. 12

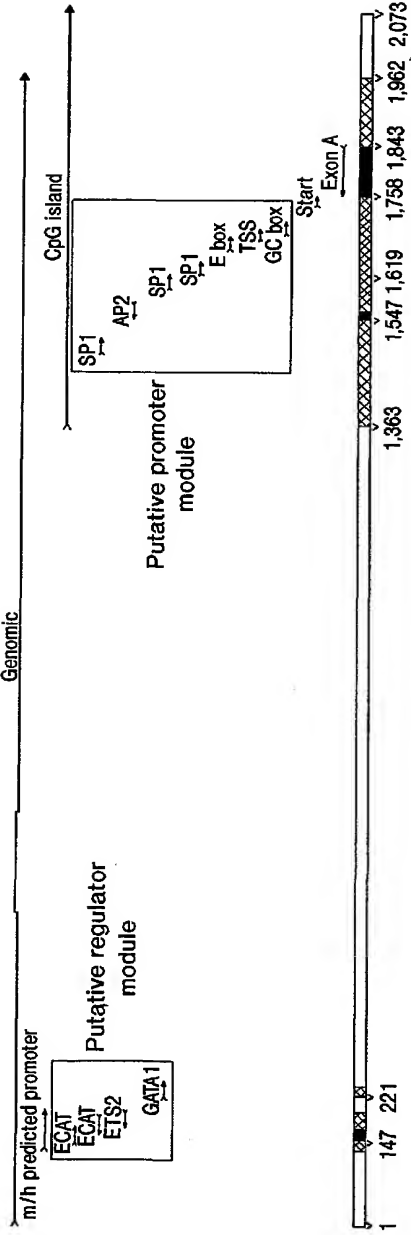


FIG. 13

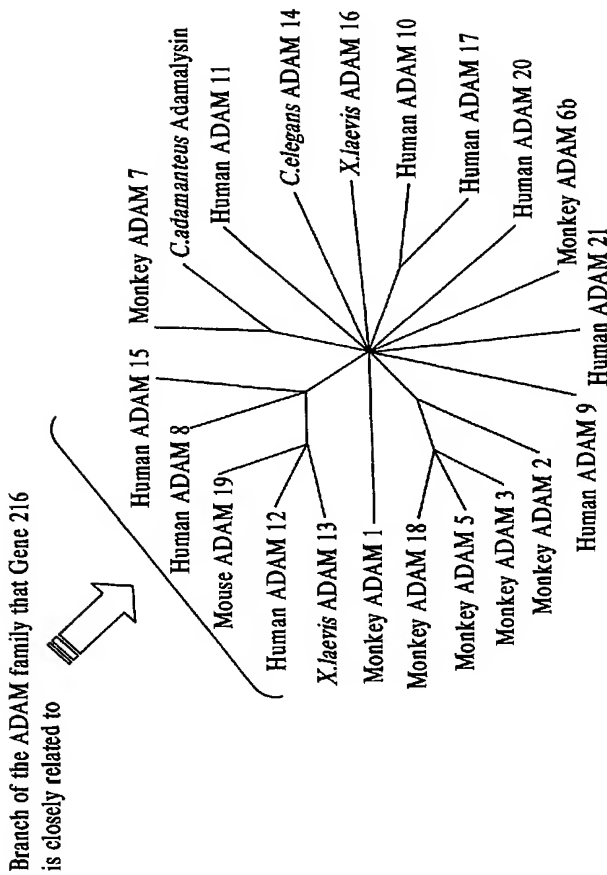


FIG. 14

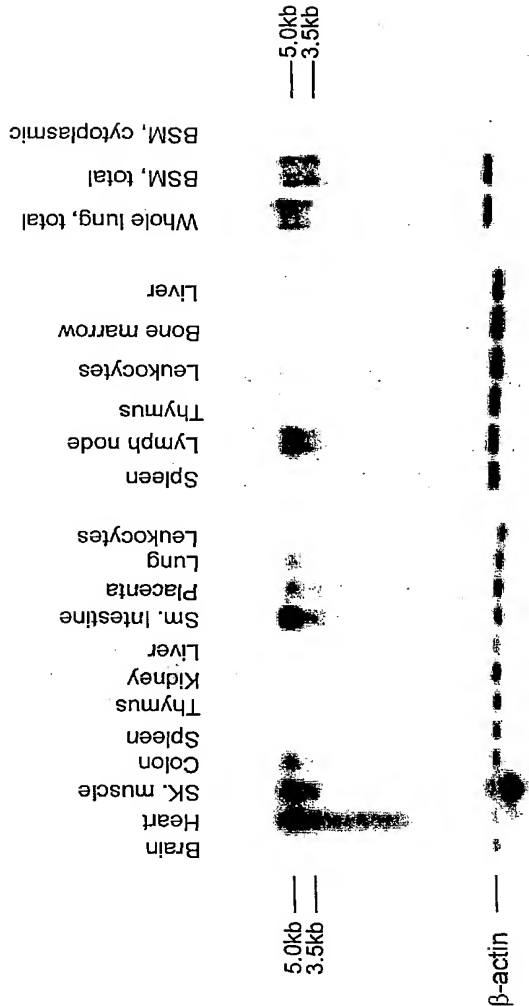


FIG. 15

	1	2	3	4	5	6	7	8
A	Whole brain	Amygdala	Caudate nucleus	Cerebellum	Cerebral cortex	Frontal lobe	Hippocampus	Medulla oblongata
B	Occipital lobe	Putamen	Substantia nigra	Temporal lobe	Thalamus	Nucleus accumbens	Spinal cord	
C	Heart	Aorta	Skeletal muscle	Colon	Bladder	Uterus	Prostate	Stomach
D	Testis	Ovary	Pancreas	Pituitary gland	Adrenal gland	Thyroid gland	Salivary gland	Mammary gland
E	Kidney	Liver	Small Intestine	Spleen	Thymus	Peripheral leukocyte	Lymph node	Bone marrow
F	Appendix	Lung	Trachea	Placenta				
G	Fetal brain	Fetal heart	Fetal kidney	Fetal liver	Fetal spleen	Fetal thymus	Fetal lung	
H	Yeast total RNA 100ng	Yeast tRNA 100ng	E.coli rRNA 100ng	E.coli DNA 100ng	Poly (A) 100ng	Human Cot1 DNA 100ng	Human DNA 100ng	Human DNA 500ng

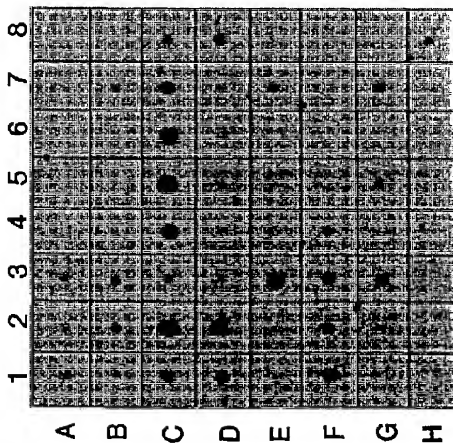


FIG. 16

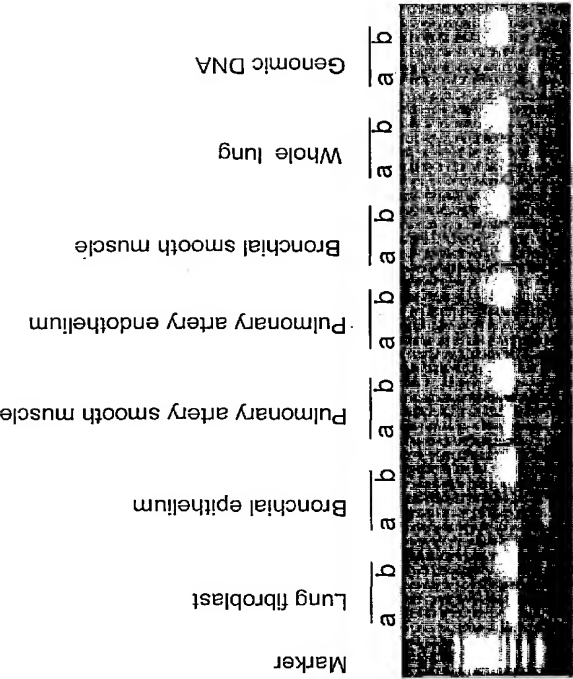
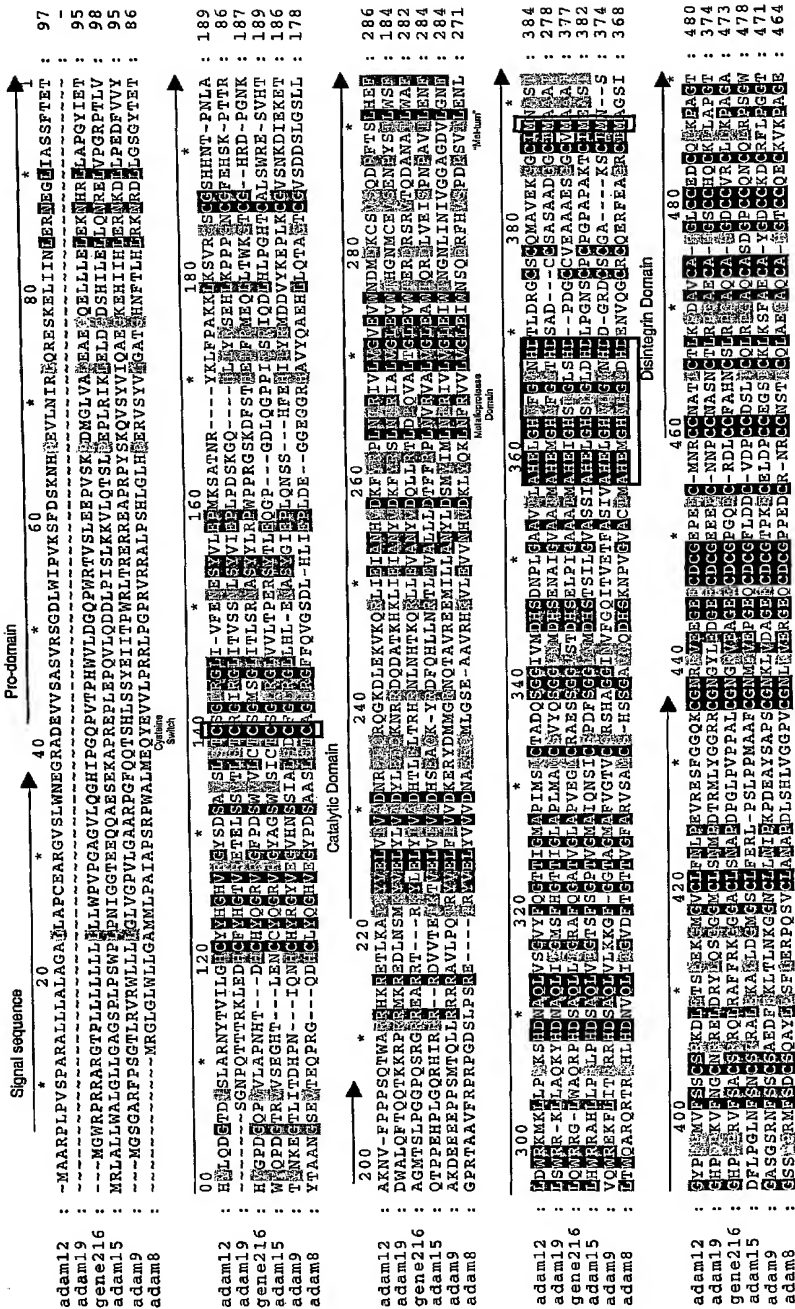
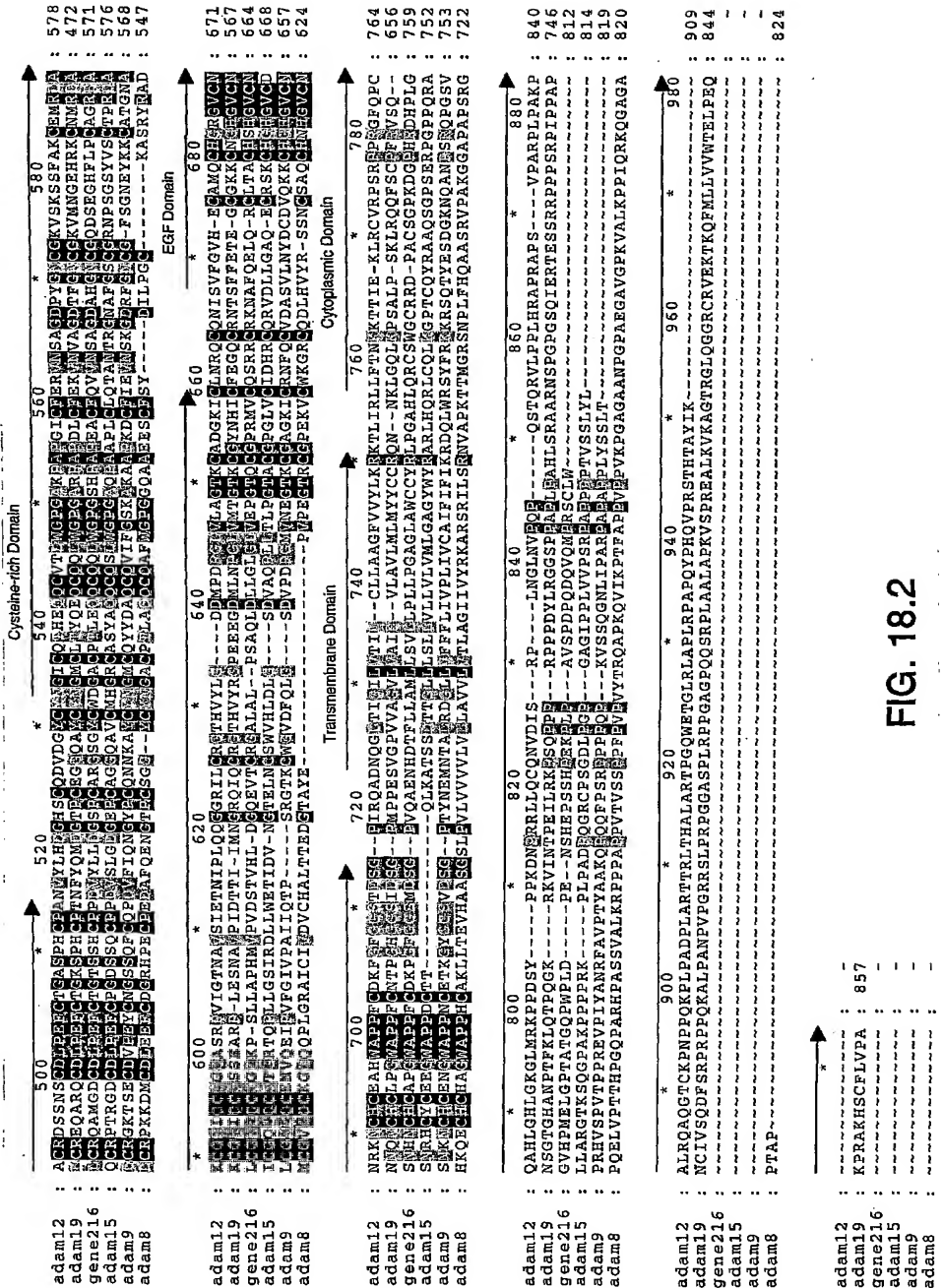


FIG. 17





**FIG. 18.1**



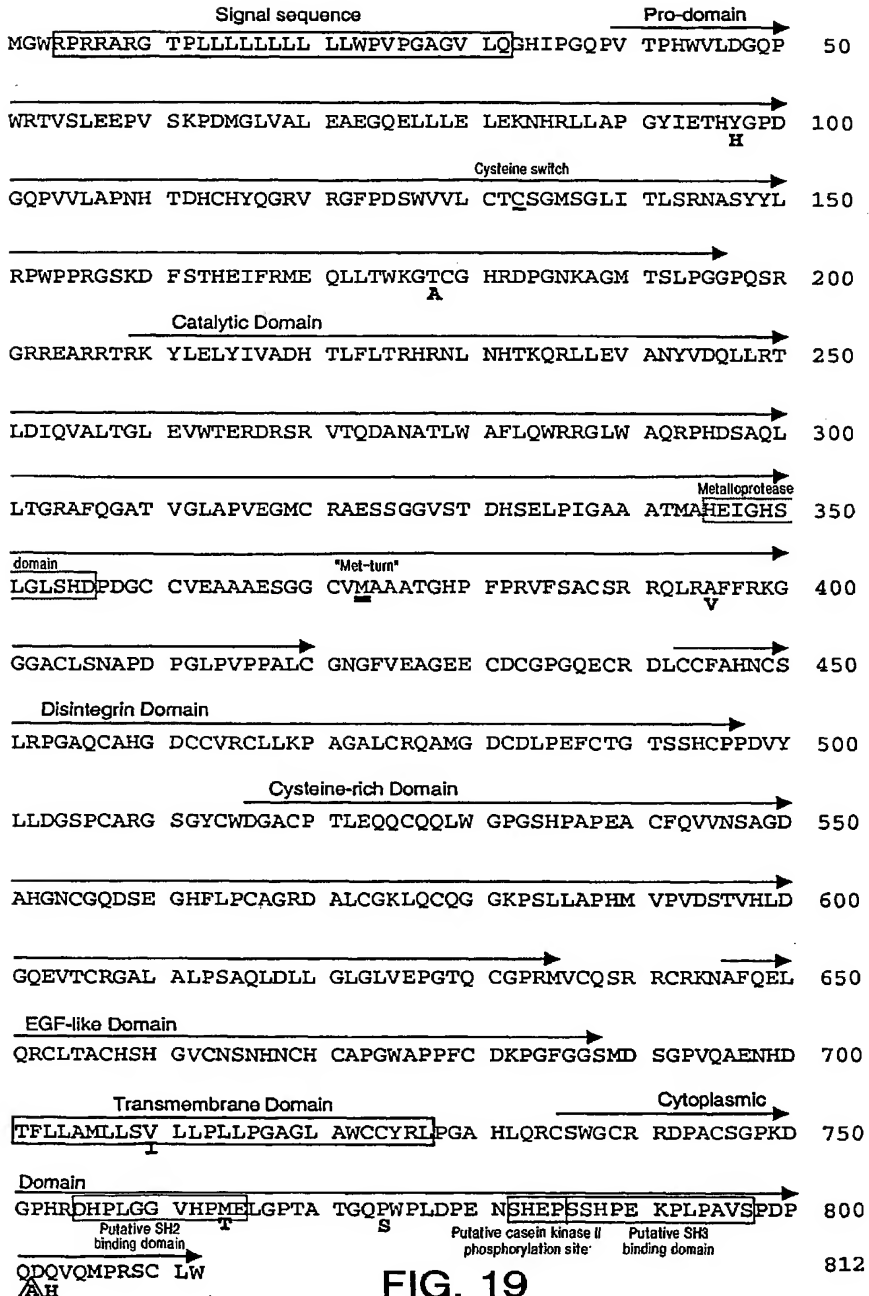


FIG. 19

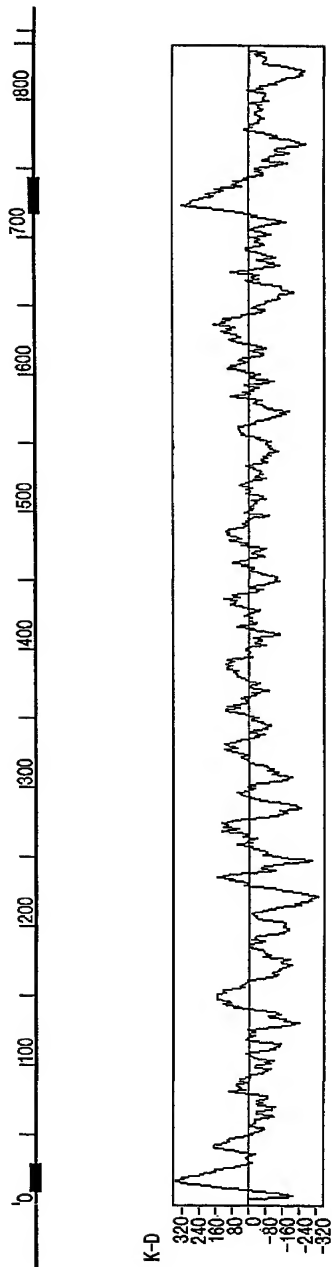


FIG. 20

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 ctccctagctatccctccctccctcccttacttctatcttccctcttcttcttccctccct  
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FIG. 21.1

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FIG. 21.2

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FIG. 21.3

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FIG. 21.4



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tgatccttgggtcctccttggggcccgactgcccgattttagcgtcacagcctcctgtct  
ccagttcctaggctcctctctctctcgattgctcgttagcttagaaagaaacagcacat  
cttgagggtctgtgtgctaacctcagggccagagtgacagaagtgcctgagcttaggag  
gtggctccagcaccgcagatgggtccccacaccacaaatgacatcttccatctgcag  
gcacctttcccgcgcgctcttcagcgctgcagcgccggcagctgcgcaccttctccg  
caaggggggcggtccttgctctccaacacctcggcgccggggctcctgggtgctgccag  
ccgctgcggaaacggcttcttgaagcaggagaagagtgcgactgcgggttctggccaggt  
cagatcgtcatcttcgctcctgggttcaaggctaaccatgctcccagccttcccagg  
tctagcttgcctccaccatcacgtgttctgttctctccttctgacttcagaagtgccag  
accctgctgctttgccacaattgctccctgcgtgcgggggctcaatgtgccacgggtg  
attgctgtgcgaggtgcctggtaggatactggggagcgccctgtacatcttagctgggc  
tgggacttctagtcccttttctgagtgtgagtttgaccagtgatgggttcacgtagca

FIG. 21.5

ctccctcgggctttcagcaaatgctctctgctttcccttaatgggtctctgggtgtagtt  
aaagtccgcgggcacgccttgtcgtcctgctgcgactgactgcgatctccccgagttctg  
caccggcacctccccctattgccccgcagatgtttacctactggatgggtcacctcgcc  
tgagggctcgggctattgcctagacggctggtgtcccacgctggagcagcagtgccagca  
gctatgggggctggtgagaccgcacgctggtcctgggtgccctgaccaatactaaaacct  
gcggttttctactgagggcaagctccacccgtggaactgagggccgagctgcccgcttct  
tactccccctcccccgagggtccaagccggccccagagcatggtttccagcagatgaact  
ccatggggaattcgcaagggaactgtggccaggaccacaagggtagcttctgccttgtg  
ctcagaggtgaggtgtgatgctgagggctctgcagctgttaaagttagggcgagcatgcgga  
gggaacactccaagttgttgaccaccttccacttctccccaggggacgctctgtgtggga  
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ccacaattctcctagagggccgcgaagtgggttgcgaggggcttgggtctcccagata  
gtcacctggaccagcttgacttgggtctggttagagccaggcaccggctgtggacctagaa  
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cctcactgccagtgggcacaatgccataggtgtgcccaggacaggcactgtcagaatgc  
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cctccacagaccgagatgccttcccccttggccatgctcctcagcttctgtgctcctgtgc  
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cctcagggtccctcggtgctagccaaggaccccttTgtgctccctataaaactggccagct  
atagtgtTgctcttTctgtgccaggactctgtgcctctgtccccctgtagatcacagtgt  
gtaaacccaattTcttggcaggcagaaatgccacctgatagcacacattatctaccgagg  
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gaagtgttctagaccaattgagggaaggcagggttgggttggagatgtgactagagggc  
acctcaggccagaaacagcaccagcaggccccaggagccagtgagacggctcggggaaag  
ccaggtagtgctgggggtggggcggtgtctgcagacagggaacagggtggagtga  
gttgggagggggcacttcagaggggtggcagctgcacaccgttatcgggatagggtgtca  
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ccgggcagttcagagttcagactggcagagcacggctaaacgggacagtggaagtcacag  
ttcccccaaggagacatctctgcacttcagctctagggtgggccctcggtgacgcctac  
atctagactgagtggggctggagtggagtccctcgggagaaaggatgtccacagccct  
ggaggccctgggacataagtgaggtctggacatcttaaggacagaaacaggaatgtggaat  
tgcgaagcttgagtggaaatggagaagcaatcccccttTgtctccataacacggcacttcca  
accttctgaactcttatctgggtctgtcactggccccctgcagagacataacccctgggcagt  
gtgcatccgggtggagtttggctccatcatcactggagagccctcgccccctcgtaagtgt  
gcccccttgggacatggagaggggaagcaagggtgggtgcttgcctctgcctccttctaa  
atgctctccttaacacaccttcaatcctctgcctgctcagcccatggacctcttgcca

FIG. 21.6

acagcgttcgcaccctccatctcttgacttgctctcagaccctgcgaactctgagcttac  
ctaagaactaccctctgaagcagcctgggtctacagattgagttccagacctgccctatcc  
ctatggtaggaagcaccctgaggacctcctgttgccagtcacctacctctgtctcagt  
ttgttgctcccctcctcagatttacaggcttgcatacaataaagaaatgagacatgggctc  
agagaagctgttgtcatagagaccatgatgctggaagccctaggggcagggaaaggagac  
actgtgggttcttcttggttcttatagagggaggacaaatgtgccctgccatgtgacttg  
cagtcctcagtttctcagacgcactcttataattcctatgggctgtatgtctgagctctta  
ctcagcataggaaccccagagcccgatcatgttggtatcccgcctgccctgagagctgtgc  
tattctgaaatgttagaatgtatcttaataacaataaaatccacaagttatatcagtgttg  
tggctgtgacctgtttaaagggtctaagttgtttattaaaaagatatggagatggattac  
tgagaaagaaattagaacaacatctggacagtggaggagccagcactggggaggaaagg  
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ccctcacccctggatgtctgttagcaagggaatcagtcagtgctcagctctgttaacatc  
tgtgagaggggaaaggctgctgcagacatggcctgagcagcatctggattcgaacatttg  
cactttagggcctgctctctcccctgggtggggcactcgccattcattgcctttacgaca  
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actaccaatatataactaataatgtgtataaaatatataacacagtcacacatatataagta  
catagatgttagtacatataaatattatatatatataataattgtaattaatattactt  
aattttattttatcatttgatattatttactgttagttataacaatgtgcataatata  
gtgtaatatataaaatataattttattatatttaattattatatataaatttaattaatata  
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gccatcaaggagaagctaaaagccagcaagtgatcttctcctgagacggttctgccatggac  
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agattcctgctattaatatgcttttctcctggattatttaaatatatataacaatcactagg  
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caaggccagcctggactacagagtgagttccaggacagccagggctactcagagaaactc  
tgtcttggaaaaaaagaggaagaaagaaaaagatttattttattttatatacat  
atgagtacaccatcagacacacaagaagaggccaccagacccattacagatggttgtga  
gccaccatgtggttgctgggaattgaaactcaggacctctggagacacattctgggtgctct  
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aagtcttcttaatatgaaaactcaataagaactctgccagcttctcaagtgtcatgagt  
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ccagataattactcctaataatagatgtcatgtgaatatctgtgtgtaaaacttatttatg  
tttgaacttccagtgaacttttgtttaaaaaaggggggggttgaaaaagccatgtgatc  
tattctcctagaaaagggtacagaagactaagaaagattacattggagatgtaaccttggga  
gagaaagctttggggagcaagagcatagagagcaaggccatttgtggcatcagagcaggagg

FIG. 21.7

agagagcaagattagaaggagatgcagagtggaataacttagaaaactataaggcaacata  
aaaaattaagagagccatatgcagaatgcagagggaaagagaaaaaaaaaaaaaaga  
agctgcaggagagcagaaggagcaggcaggtctctcctgaccatggggtagaacagggc  
tttctttaataccaaggcaggttagtcttaaggataataaaagcttttctttcttacaga  
cttggttttaattcatttagcaataaaaagtgtaaaagtgtttctttccctatgcaataa  
agattggagcttatttttcagccagaatgagtgagttctctctgcaacgggtgcttggtct  
tttgcttcataacacacataagtgtgtgtgtgcgcgcgatcgctgtgtgtgtgtgtgt  
gtgtgtgtgtgtgtaagtgtgcaattatcagatggcatggaagctgggctcaattgggtc  
aaatggggacttggtgagggtatatgcatgaatctgtatatgaattcctgtgagcttatat  
atatttgcttggtgtaaaaagttttctctgtgagtggtgactctctctcctggttcaat  
agaggtttattgcttcaaacttccccctagcctgacagtcgagaggcatctggacaagag  
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gaaactgttttagagagaacatagaaacaggctgaaatcacttgtcaaactgtcccctttt  
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gcaaaagttaaagcatgagctgaaactagtaaagtgttggtgtggcatagaccaagacctg  
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gcaaaagctcccagcaagacaaaactacagtcttcataggagagtggtgcacgctgaagacc  
gagcacactgggtgcaaaatgtacttggttctgtttgcttggtttgttccagacagggt  
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aacctcagagatccgttcacccaagccttatctaggcttcagctctcacctgtgagatgg  
cctgaaagtgtgttagaaccgcgcgggatctatttctgacagactggctggcatcttttcc  
ttctctcagcatgagattcctggggcggtcccatctcagcatcaagcatggtagcagagt  
tggaacctgagggtgagggctcagactcagaccataaactggaagcagagagaactgga  
gattgtgggaggttttgaacctcagctcctgccccagcaaataccttccagcaaggcca  
cacctcttaaacctccccaaacagggtcaccaactggggacctaatattcaaatgccac  
aaatatgggagacatgacatccaaacggccaggacaggtgtatacctccatgcttggttt  
ccgtagtaagaaacactaaacattagcctttcctaataaacactgatataaagccctgct  
attctcgatgttttctctgttctgctcctcctcctccagcaaataccttctgttctctga  
cctctctgtgtacagatagccctgccatgtccatctgccagccatgttctgtctactt  
gcctctctctctgctctggactcttctagatgcctctggctgttctttctcatatctaca

FIG. 21.8

>m216\_cDNA  
 AAAGGCACCTCCAGCCATGGGCTCGAGGTGCGGGAGACCCGGGGGGTCTCCG  
 GTGCTGCTATTGCTGCCGCTGTGCTGCCCTCGTGTCGGTGC GGAGCGCTCG  
 GATGTTTCCAGGAAATGCCCATGGAGAGCTAGTCACCTCCCCACTGGATCCCTGG  
 AGGGCAGACTTGGCTCAAGGTACCCCTGGAGGAGCCGATCTTTGAAGCCTGAC  
 TCGGTGCTGGTGGCTTTAGAGGCTGAAGGCAGGATCTCTGCTTGAACCTGGA  
 GAAGAAGCACAGCTTCTGGCCCCAGGATACACAGAAACCCACTACAGGCCAG  
 ATGGGCATCCGGTAGTGCTGTCCCCCAACCACACGGATCATTTGCCAATATCAC  
 GGGCGTGTGAGGGGCTTCCGGGAACTCTGGGTGGTTCTCAGCACCTGCTCTG  
 GGATGAGTGGCCTTATTGTGCTCAGCAGCAAAGTCAGCTATTATCTGCAACCTC  
 GGACTCCTGGGGATACCAAGACTTCCCAACCACAGAGATCTTCCGGATGGAG  
 CAGTTGTTACCTGGAGAGGGGTCCAGAGAGACAAGAACCTCCCAATACAAAGC  
 AGGAATGGCCAGTCTTCTCATGTCCCCACAGCCGGGTGAGGGCAGAGGGC  
 CGCAGAGGTCCCAAGGTACCTGGAACGTGTACATAGTGGCTGACCACACCTGAA  
 CTTGAAACACACAGAGACAGCGCTCTCTGGAGGTGCCAATTGCGGTGGACCAGA  
 TTCTCAGGACTCTGGATATACAGTTGGTGTGACCGGGCTGGAAGTGTGGACC  
 GAGCAGGATCTCAGTCGCATCACTCAGGACGCCAAACGAAACGCTCTGGGCTTT  
 CCTACAGTGGCGCCCGCGGGGTGTGGGCCAGGAGACACACGACTCCACACAA  
 CTGCTCAGGGGCCACCTTCCAGGGTACCACGGTGGGCTTGGCACTGTGTTG  
 AGGGCATATGCCGCGCGGAGAGCTCCGGAGGTGTGAGCACAGACCACCTCGGA  
 ACTCCCCATCGGCACAGCAGCCACCATGGCCCCACGAGATAGGCCACAGCCCTGG  
 GCCTCCACCATGATCCCGAGGGCTGCTGCGTGCAGGCCGATGACAGAGCAAGG  
 AGGCTGGGTCTAGGAGGCAGCCACAGGGCACCTTTCCCGCGCGTCTTCAGGG  
 CCTGCAGCCGCCCGCAGCTGCGCACCTTCTTCCGCAAGGGGGCGGTCTCTGCT  
 CTCCTCAACACCTCGGCCCGGGGGCTCTGGTGTCTGCCAGCCGCTGCGGGAAA  
 CGGCTTCTTGGAAAGCAGGAGAAGAGTGCAGACTGCGGTCTTGGCCAGAAAGTGC  
 CCGGACCCCTGCTGCTTTGCCACAATTGCTCCCTGCGTGGGGGGCTCAATGT  
 TGCCCCACGGTGATTGCTGTGCGAAGTGTGTTAAAGTCCGCGGCCACGCCCTT  
 GTGCTCTGCTGCGACTGACTGCGATCTCCCCAGTTCTGCAACCGGCACCTCC  
 CCGTATTGCCCCGACAGATGTTTACCTACTGGATGGCTCACCTCTGCGTGGAGG  
 TCGCGGCTATTGCCCTAGACGGCTGGTGTGCCACGCTGGAGCAGCAGTGCACGC  
 AGCTATGGGGGCTGGGTCCAAGCCGGCCCCAGAGCCATGTTTCCAGCAGAT  
 GAACTCCATGGGGAATTGCAAGGGAACCTGTGGCCAGGACCACAAGGGTAGC  
 TTCTCTGCTTGTGCTCAGAGGGAAGCTCTGTGTGGGAAACTGCTGTGCCAGGG  
 AGGGAGGCCGAACCCACTAGTGCCCGCACATAGTGACTATGGACTCCACAATTCT  
 TCCTAGAGGGCCGCCGAAGTGGTTTGCCGAGGGGCTTTGTGCTCCCAAGATGT  
 CACCTGGACCAGCTTGACTTGGGTCTGGTAGAGCCAGGCACCGGCTGTGGACC  
 TAGAATGGTGTGCCAGGACAGGCATGTGAGAAATGCTACCTCCAGGAGCTGG  
 AACGTTGCTTTGACTGCTGCCATAACGGTGGGGTTTGCAATAGCAATCGTAAC  
 GTCACTGTGCTGCTGGCTGGGCTCCACCTTCTGTGACAAGCTGGCTTGGGT  
 GGTAGCGTGGATAGTGGCCCTGCACAGTCTGCAAAACGAGATGCTTCCCCCTT  
 GGCATGCTCTCTCAGCTTCTCTGCTGCTCTGCTCCCTGGGGCTGGCCTAGCCT  
 GGTGCTACTACAGCTCCCAACATTCTGTGATCGAAGGGGACTGTGCTGCAGG  
 AGGACCCCCCTATGGAATAGAGACATAACCTTGGCAGTGTGCTGCTGGTGA  
 GTTTGGCTCCATCATCACTGGAGAGCCCTCGCCCCCTCCCCATGGACCTCTTG  
 CCAACAGCGTTTCGCACCTTCCATCTCTGACTTGCTCTCAGACCTCGCAACTC  
 TGAGCTTACCTAAGAACTACCTCTGAAGCAGCTGGTCTACAGATTGAGTTTC  
 AGACCTGCCCCATCCCTATGGTATGGAAGCACCTGAGGACCTCTCTGTGCCCA  
 GTCACCTACCTCTGTCTCAGTTTGTGTGCCCTCTCAGATTACAGGCTTGAT  
 CAATAAAGAAATGAGACATGGGCCCTCAGAGAASCTGTTGTATAGAGACCATG  
 ATGCTGGAAACCCCTAGGGGCAGGGAAGGGAGACACTGTGGTTCTTCTTGGGTC  
 CTTATAGAGGGAGGACAAATGTGCCCTGCCATGTGACTTGCAAGTCTCAGTTTC  
 TCAGACGCACTCTTAATAATCCCTATGGGCTGTATGCTGAGCTCTTACTCAGCAT  
 GGAACCCAGAGCCCGATCATGTTGTATCCCSCTGCGCTGAGAGCTGTGCTAT  
 TCTGAAATGTTAGAATGTATCTAATAACAATAAATCCCAAGTTATATCAGHAAA  
 AAAAAAA

FIG. 22.1

>m216\_protein

MGSRRCGRPGGSPVLLLLPLLLPSCPLRSARMFPGNAHGELVTPHWILEGRLWLKVTLEEPILKPDSVLVALEAEGQDLLL  
ELEKKHKLLAPGYTETHYRPDGHFVVLSPNHTDHCQYHGRVGRGFRESWVLSTCSGMSGLIVLSSKVSYYLQPRTPGDTK  
DFPTHEIFRMEQLFTWRGVQRDKNSQYKAGMASLPHVPQSRVRREARRSPRYLELYIVADHTLNLNHTQRLLLEVANCVD  
QILRTLDIQLVLTGLEVWTEQDLSRITQDANETLWAFLOWRRGVWARRPHDSTQLLTGRTFQGTTVGLAPVEGICRAESS  
GGVSTDHSELPIGTAATMAHEIGHSLGLHHDEGCCVQADAEQGGCVMEAATGHFFPRVFSACSRRLRTFFRKGGGPCL  
SNTSAPQLLVLPSCGNGFLEAGEECDGSGQKCPDFCCFAHNCSLRAGAQCAGDCCAKCLLKSACTPCRPAATDCDLP  
EFCTGTSPYCPADVYLLDGSPCAEGRGYCLDGWCPTLEQQCQQLWGP GSKPAPEPCFQQMNSMGNSQGNCGQDHKGSFLP  
CAQRDALCGKLLCQGGEPNPLVPHIVTMDSTILLEGREVVCRGAFVLPDSHLDDLDLGLVEPGTGCGRMVCQDRHCQNA  
TSQELERCLTACHNGGVCNSNRNCHCAAGWAPFFCDKPGLGGSVDSGPAQSANRDAFPLAMLLSFLLPLLPAGGLAWCY  
QLFTFCHRRGLCCRRDPLWNRDIPLGSVHPVEFGSIITGEFSPPPPWTSCQQRSHPPSLDLLSDPANSELT

FIG. 22.2

FIG. 23.1





```

      10                               30                               50
CGGGCACGGGTCGGCCGCAATCCAGCCTGGGCGGAGCCCGAGTTGCGAGCCGCTGCCTAG
-----+-----+-----+-----+-----+-----+-----+
      70                               90                               110
AGGCCGAGGAGCTCACAGCTATGGGCTGGAGGCCCGGAGAGCTCGGGGGACCCCGTTGC
-----+-----+-----+-----+-----+-----+
                               MetGlyTrpArgProArgArgAlaArgGlyThrProLeuL
      130                               150                               170
TGCTGCTGCTACTACTGCTGCTGCTCTGGCCAGTGCCAGGCGCCGGGGTGCTTCAAGGAC
-----+-----+-----+-----+-----+-----+
euLeuLeuLeuLeuLeuLeuLeuLeuLeuTrpProValProGlyAlaGlyValLeuGlnGlyH
      190                               210                               230
ATATCCCTGGGCAGCCAGTCACCCCGCAC TGGGTCTTGGATGGACAACCTTGGCGCACCG
-----+-----+-----+-----+-----+-----+
isIleProGlyGlnProValThrProHisTrpValLeuAspGlyGlnProTrpArgThrV
      250                               270                               290
TCAGCCTGGAGGAGCCGGTCTCGAAGCCAGACATGGGGCTGGTGGCCCTGGAGGCTGAAG
-----+-----+-----+-----+-----+-----+
alSerLeuGluGluProValSerLysProAspMetGlyLeuValAlaLeuGluAlaGluG
      310                               330                               350
GCCAGGAGCTCCTGCTTGAGCTGGAGAAGAACCCACAGGCTGCTGGCCCCAGGATACATAG
-----+-----+-----+-----+-----+-----+
lyGlnGluLeuLeuLeuGluLeuGluLysAsnHisArgLeuLeuAlaProGlyTyrIleG
      370                               390                               410
AAACCCACTACGGCCCAGATGGGCAGCCAGTGGTGTGGCCCCAACCCACCGGTGAGAT
-----+-----+-----+-----+-----+-----+
luThrHisTyrGlyProAspGlyGlnProValValLeuAlaProAsnHisThrValArgC
      430                               450                               470
GCTTCCATGGGCTCTGGGATGCACCGCCAGAGGATCATTGCCACTACCAAGGGCGAGTAA
-----+-----+-----+-----+-----+-----+
ysPheHisGlyLeuTrpAspAlaProProGluAspHisCysHisTyrGlnGlyArgValA

```

FIG. 24.1

```

      490              510              530
      .               .               .
GGGGCTTCCCGACTCCTGGGTAGTCCTCTGCACCTGCTCTGGGATGAGTGGCCTGATCA
-----+-----+-----+-----+-----+-----+-----+
rgGlyPheProAspSerTrpValValLeuCysThrCysSerGlyMetSerGlyLeuIleT

      550              570              590
      .               .               .
CCCTCAGCAGGAATGCCAGCTATTATCTGCGTCCCTGGCCACCCCGGGGCTCCAAGGACT
-----+-----+-----+-----+-----+-----+-----+
hrLeuSerArgAsnAlaSerTyrTyrLeuArgProTrpProProArgGlySerLysAspP

      610              630              650
      .               .               .
TCTCAACCCACGAGATCTTTCGGATGGAGCAGCTGCTCACTGGAAAGGAACCTGTGGCC
-----+-----+-----+-----+-----+-----+-----+
heSerThrHisGluIlePheArgMetGluGlnLeuLeuThrTrpLysGlyThrCysGlyH

      670              690              710
      .               .               .
ACAGGGATCCTGGGAACAAAGCGGGCATGACCAGCCTTCTGGTGGTCCCCAGAGCAGGG
-----+-----+-----+-----+-----+-----+-----+
isArgAspProGlyAsnLysAlaGlyMetThrSerLeuProGlyGlyProGlnSerArgG

      730              750              770
      .               .               .
GCAGGCGAGAAGCGCGCAGGACCCGGAAGTACCTGGAACCTGTACATTGTGGCAGACCACA
-----+-----+-----+-----+-----+-----+-----+
lyArgArgGluAlaArgArgThrArgLysTyrLeuGluLeuTyrIleValAlaAspHist

      790              810              830
      .               .               .
CCCTGTCTTGTGACTCGGCACCGAAACTTGAACCACACCAAACAGCGTCTCCTGGAAGTCG
-----+-----+-----+-----+-----+-----+-----+
hrLeuPheLeuThrArgHisArgAsnLeuAsnHisThrLysGlnArgLeuLeuGluValA

      850              870              890
      .               .               .
CCAACTACGTGGACCAAGCTTCTCAGGACTCTGGACATTACAGGTGGCGCTGACCGGCCTGG
-----+-----+-----+-----+-----+-----+-----+
laAsnTyrValAspGlnLeuLeuArgThrLeuAspIleGlnValAlaLeuThrGlyLeuG

      910              930              950
      .               .               .
AGGTGTGGACCGAGCGGGACCGCAGCCGCTCACGCAGGACGCCAACGCCACGCTCTGGG
-----+-----+-----+-----+-----+-----+-----+
luValTrpThrGluArgAspArgSerArgValThrGlnAspAlaAsnAlaThrLeuTrpA

      970              990             1010

```

FIG. 24.2

```

CCTTCTGCAGTGGCGCCGGGGCTGTGGGCGCAGCGGCCACGACTCCGCGCAGCTGC
-----+-----+-----+-----+-----+-----+-----+-----+
1aPheLeuGlnTrpArgArgGlyLeuTrpAlaGlnArgProHisAspSerAlaGlnLeuL

      1030              1050              1070
TCACGGGCCGCGCCTTCCAGGGCGCCACAGTGGGCCTGGCGCCCGTCGAGGGCATGTGCC
-----+-----+-----+-----+-----+-----+-----+
euThrGlyArgAlaPheGlnGlyAlaThrValGlyLeuAlaProValGluGlyMetCysA

      1090              1110              1130
GCGCCGAGAGCTCGGGAGGCGTGAGCACGGACCACTCGGAGCTCCCCATCGGCGCCGAG
-----+-----+-----+-----+-----+-----+-----+
rgAlaGluSerSerGlyGlyValSerThrAspHisSerGluLeuProIleGlyAlaAlaA

      1150              1170              1190
CCACCATGGCCCATGAGATCGGCCACAGCCTCGGCCTCAGCCACGACCCGACGGCTGCT
-----+-----+-----+-----+-----+-----+-----+
1aThrMetAlaHisGluIleGlyHisSerLeuGlyLeuSerHisAspProAspGlyCysC

      1210              1230              1250
GCGTGGAGGCTGCGGCCGAGTCCGGAGGCTGCGTCATGGCTGCGGCCACCGGGCACCCGT
-----+-----+-----+-----+-----+-----+-----+
ysValGluAlaAlaAlaGluSerGlyGlyCysValMetAlaAlaAlaThrGlyHisProP

      1270              1290              1310
TTCCGCGCGTGTTCAGCGCCTGCAGCCGCGCCAGCTGCGCGCCTTCTTCCGCAAGGGGG
-----+-----+-----+-----+-----+-----+-----+
heProArgValPheSerAlaCysSerArgArgGlnLeuArgAlaPhePheArgLysGlyG

      1330              1350              1370
GCGGCGCTTGCCCTCTCCAATGCCCCGGACCCGGACTCCCGGTGCCGCCGCGCTCTGCG
-----+-----+-----+-----+-----+-----+-----+
lyGlyAlaCysLeuSerAsnAlaProAspProGlyLeuProValProProAlaLeuCysG

      1390              1410              1430
GGAACGGCTTCGTGGAAGCGGGCGAGGAGTGTGACTGCGGCCCTGGCCAGGAGTGCCGCG
-----+-----+-----+-----+-----+-----+-----+
lyAsnGlyPheValGluAlaGlyGluGluCysAspCysGlyProGlyGlnGluCysArgA

      1450              1470              1490

```

FIG. 24.3

```

ACCTCTGCTGCTTTGCTCACAACCTGCTCGCTGCGCCCCGGGGCCCCAGTGCGCCCCACGGGG
-----+-----+-----+-----+-----+-----+
spLeuCysCysPheAlaHisAsnCysSerLeuArgProGlyAlaGlnCysAlaHisGlyA

      1510              1530              1550
ACTGCTGCGTGCCTGCTGAAGCCGGCTGGAGCGCTGTGCCGCCAGGCCATGGGTG
-----+-----+-----+-----+-----+
spCysCysValArgCysLeuLeuLysProAlaGlyAlaLeuCysArgGlnAlaMetGlyA

      1570              1590              1610
ACTGTGACCTCCCTGAGTTTTCACGGGCACCTCCTCCCACGTCCCCAGACGTTTACC
-----+-----+-----+-----+-----+
spCysAspLeuProGluPheCysThrGlyThrSerSerHisCysProProAspValTyrL

      1630              1650              1670
TACTGGACGGCTCACCCCTGTGCCAGGGGCAGTGGCTACTGCTGGGATGGCGCATGTCCCA
-----+-----+-----+-----+-----+
euLeuAspGlySerProCysAlaArgGlySerGlyTyrCysTrpAspGlyAlaCysProT

      1690              1710              1730
CGCTGGAGCAGCAGTGCCAGCAGCTCTGGGGGCCCTGGCTCCCACCCAGCTCCCGAGGCCT
-----+-----+-----+-----+-----+
hrLeuGluGlnGlnCysGlnGlnLeuTrpGlyProGlySerHisProAlaProGluAlaC

      1750              1770              1790
GTTTCCAGGTGGTGAACCTCTGCGGGAGATGCTCATGGAACTGCGGCCAGGACAGCGAGG
-----+-----+-----+-----+-----+
ysPheGlnValValAsnSerAlaGlyAspAlaHisGlyAsnCysGlyGlnAspSerGluG

      1810              1830              1850
GCCACTTCCTGCCCTGTGCAGGGAGGGATGCCCTGTGTGGGAAGCTGCAGTGCCAGGGTG
-----+-----+-----+-----+-----+
lyHisPheLeuProCysAlaGlyArgAspAlaLeuCysGlyLysLeuGlnCysGlnGlyG

      1870              1890              1910
GAAAGCCCAGCCTGCTCGCACCGCACATGGTGCCAGTGGACTCTACCGTTACCTAGATG
-----+-----+-----+-----+-----+
lyLysProSerLeuLeuAlaProHisMetValProValAspSerThrValHisLeuAspG

      1930              1950              1970
GCCAGGAAGTGACTTGTGCGGGAGCCTTGGCACTCCCCAGTGCCACAGCTGGACCTGCTTG
-----+-----+-----+-----+-----+

```

FIG. 24.4

```

-----+-----+-----+-----+-----+-----+
lyGlnGluValThrCysArgGlyAlaLeuAlaLeuProSerAlaGlnLeuAspLeuLeuG

          1990                      2010                      2030
GCCTGGGCCTGGTAGAGCCAGGCACCCAGTGTGGACCTAGAATGGTGTGCCAGAGCAGGC
-----+-----+-----+-----+-----+-----+
lyLeuGlyLeuValGluProGlyThrGlnCysGlyProArgMetValCysGlnSerArgA

          2050                      2070                      2090
GCTGCAGGAAGAATGCCTTCCAGGAGCTTCAGCGCTGCCCTGACTGCCTGCCACAGCCACG
-----+-----+-----+-----+-----+-----+
rgCysArgLysAsnAlaPheGlnGluLeuGlnArgCysLeuThrAlaCysHisSerHisG

          2110                      2130                      2150
GGGTTTGCAATAGCAACCATAACTGCCACTGTGCTCCAGCTGGGCTCCACCCCTTCTGTG
-----+-----+-----+-----+-----+-----+
lyValCysAsnSerAsnHisAsnCysHisCysAlaProGlyTrpAlaProProPheCysA

          2170                      2190                      2210
ACAAGCCAGGCTTTGGTGGCAGCATGGACAGTGGCCCTGTGCAGGCTGAAAACCATGACA
-----+-----+-----+-----+-----+-----+
spLysProGlyPheGlyGlySerMetAspSerGlyProValGlnAlaGluAsnHisAspT

          2230                      2250                      2270
CCTTCCTGCTGGCCATGCTCCTCAGCGTCCTGCTGCCTCTGCTCCCAGGGGCCGGCCTGG
-----+-----+-----+-----+-----+-----+
hrPheLeuLeuAlaMetLeuLeuSerValLeuLeuProLeuLeuProGlyAlaGlyLeuA

          2290                      2310                      2330
CCTGGTGTGTGCTACCGACTCCCAGGAGCCCATCTGCAGCGATGCAGCTGGGGCTGCAGAA
-----+-----+-----+-----+-----+-----+
laTrpCysCysTyrArgLeuProGlyAlaHisLeuGlnArgCysSerTrpGlyCysArgA

          2350                      2370                      2390
GGGACCCTGCGTGCAGTGGCCCCAAAGATGGCCACACAGGGACCACCCCTGGGCGGGC
-----+-----+-----+-----+-----+-----+
rgAspProAlaCysSerGlyProLysAspGlyProHisArgAspHisProLeuGlyGlyV

          2410                      2430                      2450
TTCACCCCATGGAGTTGGGCCCCACAGCCACTGGACAGCCCTGGCCCCCTGGACCCCTGAGA
-----+-----+-----+-----+-----+-----+

```

FIG. 24.5

alHisProMetGluLeuGlyProThrAlaThrGlyinproTrpProLeuAspProGluA

2470 2490 2510  
 ACTCTCATGAGCCAGCAGCCACCCTGAGAAGCCTCTGCCAGCAGTCTCGCCTGACCCCC  
 -----+-----+-----+-----+-----+  
 snSerHisGluProSerSerHisProGluLysProLeuProAlaValSerProAspProG

2530 2550 2570  
 AAGCAGATCAAGTCCAGATGCCAAGATCCTGCCTCTGGTGAGAGGTAGCTCCTAAATGA  
 -----+-----+-----+-----+-----+  
 lnAlaAspGlnValGlnMetProArgSerCysLeuTrpEnd

2590 2610 2630  
 ACAGATTAAAGACAGGTGGCCACTGACAGCCACTCCAGGAACCTGAACTGCAGGGGCAG  
 -----+-----+-----+-----+-----+  
 -----+-----+-----+-----+-----+

2650 2670 2690  
 AGCCAGTGAAATCACCGGACCTCCAGCACCTGCAGGCAGCTTGGAAAGTTCTTCCCCGAGT  
 -----+-----+-----+-----+-----+  
 -----+-----+-----+-----+-----+

2710 2730 2750  
 GGAGCTTCGACCCACCCACTCCAGGAACCCAGAGCCACATTAGAAGTTCTGAGGGCTGG  
 -----+-----+-----+-----+-----+  
 -----+-----+-----+-----+-----+

2770 2790 2810  
 AGAACACTGCTGGGCACACTCTCCAGCTCAATAAACCATCAGTCCAGAAGCAAAGGTCA  
 -----+-----+-----+-----+-----+  
 -----+-----+-----+-----+-----+

2830 2850 2870  
 CACAGCCCCTGACCTCCCTCACCAGTGAGGGCTGGGTAGTGCTGGCCATCCCAAAAGGGC  
 -----+-----+-----+-----+-----+  
 -----+-----+-----+-----+-----+

2890 2910 2930  
 TCTGTCTCTGGGAGTCTGGTGTGTCTCCTACATGCAATTTCACGGACCCAGCTCTGTGGA  
 -----+-----+-----+-----+-----+  
 -----+-----+-----+-----+-----+

2950 2970 2990  
 GGGCATGACTGCTGGCCAGAAGCTAGTGGTCTGGGGCCCTATGGTTCGACTGAGTCCAC  
 -----+-----+-----+-----+-----+  
 -----+-----+-----+-----+-----+

FIG. 24.6

```

      3010              3030              3050
ACTCCCTGCAGCCTGGCTGGCCTCTGCAAACAAACATAATTTTGGGGACCTTCCTTCCT
-----+-----+-----+-----+-----+-----+-----+-----+

      3070              3090              3110
GTTTCTTCCACCCCTGTCTTCTCCCTAGGTGGTTCCTGAGCCCCCACCCCCAATCCCAG
-----+-----+-----+-----+-----+-----+-----+-----+

      3130              3150              3170
TGCTACACCTGAGGTTCTGGAGCTCAGAATCTGACAGCCTCTCCCCCATTCTGTGTGTGT
-----+-----+-----+-----+-----+-----+-----+-----+

      3190              3210              3230
CGGGGGGACAGAGGGAACCATTTAAGAAAAGATACCAAAGTAGAAGTCAAAAGAAAGACA
-----+-----+-----+-----+-----+-----+-----+-----+

      3250              3270              3290
TGTTGGCTATAGGCGTGGTGGCTCATGCCTATAATCCCAGCACTTTGGGAAGCCGGGGTA
-----+-----+-----+-----+-----+-----+-----+-----+

      3310              3330              3350
GGAGGATCACCCAGAGGCCAGCAGGTCCACACCAGCCTGGGCAACACAGCAAGACACCGCA
-----+-----+-----+-----+-----+-----+-----+-----+

      3370              3390              3410
TCTACAGAAAAATTTTAAAAATTAGCTGGGCGTGGTGGTGTGTACCTGTAGGCCCTAGCTGC
-----+-----+-----+-----+-----+-----+-----+-----+

      3430              3450              3470
TCAGGAGGCTGAAGCAGGAGGATCACTTGAGCCTGAGTTCAACACTGCAGTGAGCTATGG
-----+-----+-----+-----+-----+-----+-----+-----+

      3490              3510              3530
TGGCACCACCTGCACCTCCAGCCTGGGTGACAGAGCAAGACCCTGTCTCTAAAAATAAATTTT
-----+-----+-----+-----+-----+-----+-----+-----+

      3550              3570              3590

```

FIG. 24.7

AAAAAGACATAA  
-----+-----+-----+-----+-----+-----+-----+  
3610  
AAAAAAAAAAAAAAAAAAAAAAAAAAAA  
-----+-----+-----

FIG. 24.8



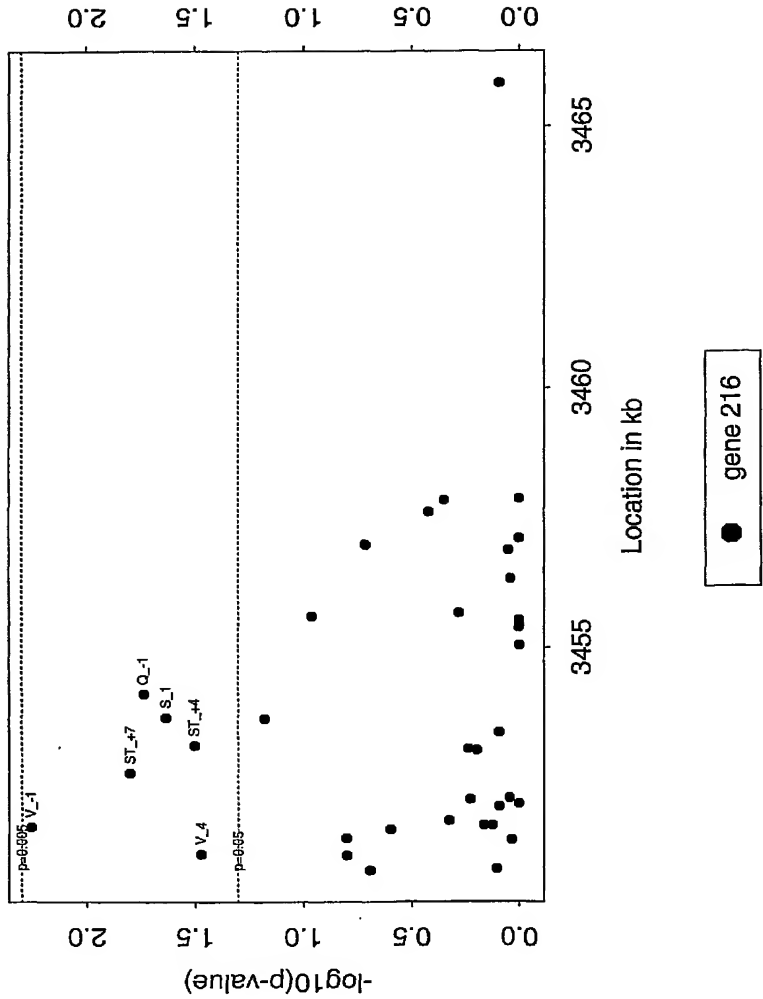
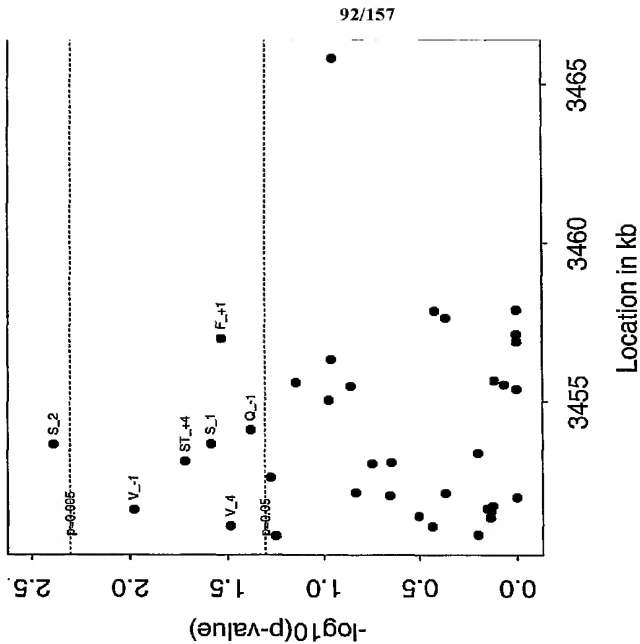


FIG. 25

UK



US

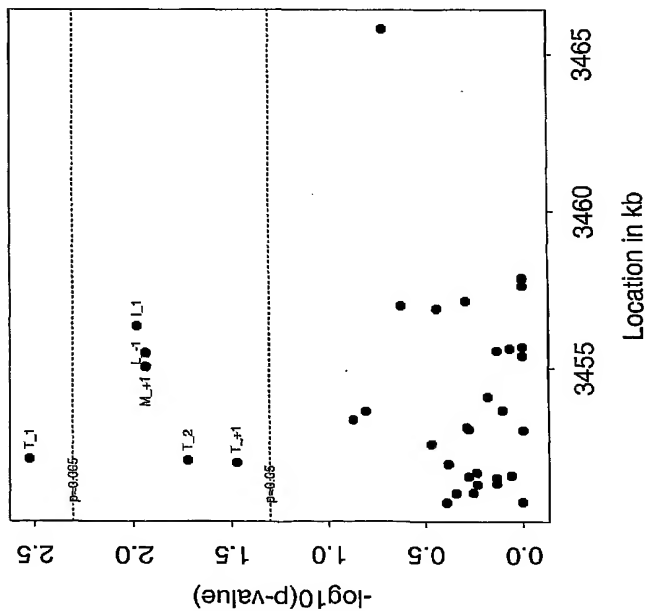


FIG. 26

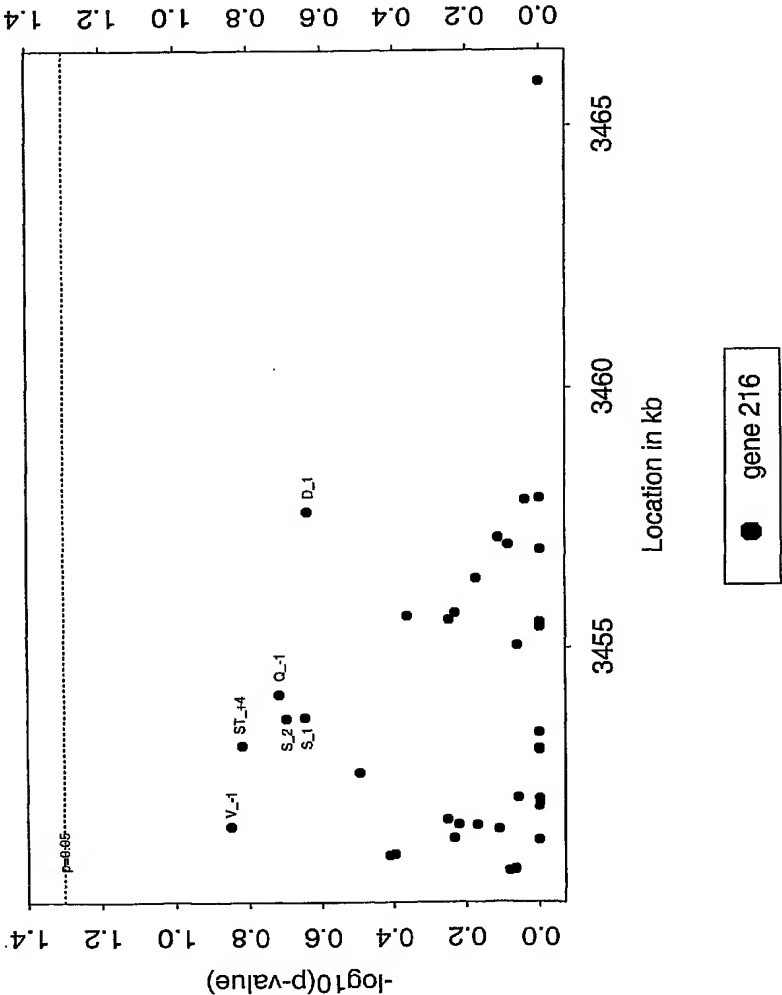
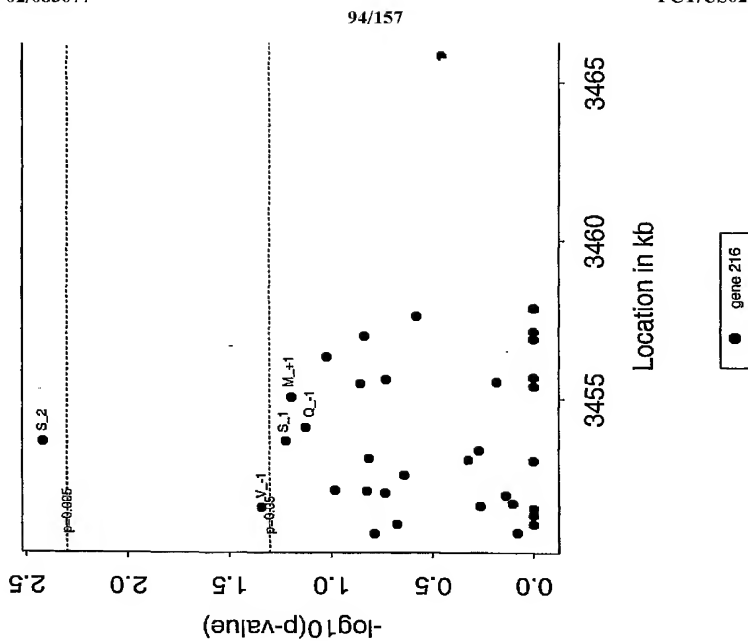


FIG. 27

UK



US

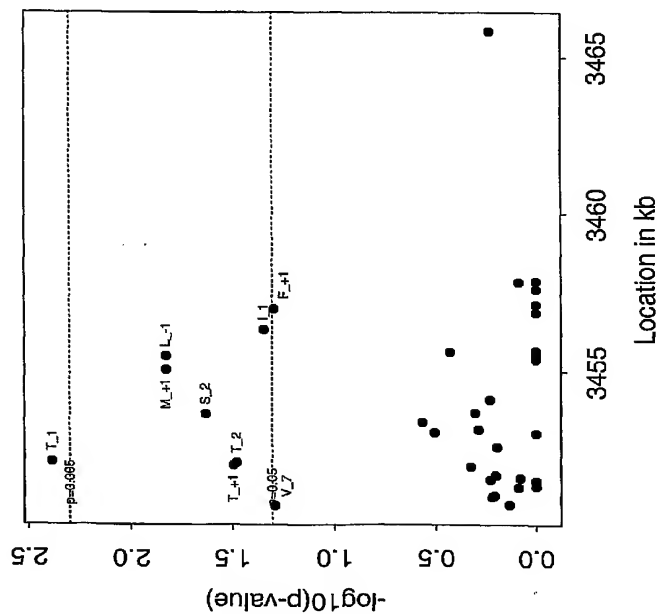


FIG. 28

**FIG. 29.1**

```

      610                      630                      650
      .                      .                      .
AGAAAAGTTACACATTATAAATGCAACTCAAGGACTTTTCCAAAAGCGAACACACCCAG
-----+-----+-----+-----+-----+-----+-----+
      670                      690                      710
      .                      .                      .
ATCAAGAAATAGACCATCCTACAGTCCCCCCTTACACTCTGTACCAGTTGCAGCCCCCAG
-----+-----+-----+-----+-----+-----+-----+
      730                      750                      770
      .                      .                      .
AAGGGTAACTACTGTCTTGACTTCGAACACCATAGATTGATTGCTGTTTTTAACTT
-----+-----+-----+-----+-----+-----+-----+
      790                      810                      830
      .                      .                      .
TACATAAGTAGAATCACAGAGTGTGTACAATGACTTTGGAAAACGTTTGACAATATCTA
-----+-----+-----+-----+-----+-----+-----+
      850                      870                      890
      .                      .                      .
TTAAAGCTAAAATACCCCTTGCCCTATGAACCTGAAATTCACCCACCTTGCCAAGGGACA
-----+-----+-----+-----+-----+-----+-----+
      910                      930                      950
      .                      .                      .
AAAAGTTCCTCTAAATGCACCAGGCTGTACAGGATGAAGCGTTGGCTTTGGGGCCCCC
-----+-----+-----+-----+-----+-----+-----+
      970                      990                      1010
      .                      .                      .
ATTACACACATGACCTTTTCTGGGGCACCCAGCATCAGCCTGTCGTCACCAGGTGCCA
-----+-----+-----+-----+-----+-----+-----+
      1030                     1050                     1070
      .                      .                      .
CCCTGGCGATCTCTGAAGGCTGGAGTCGGAGTGCCTCCCTCAGACATCCTGTTCTGCGTC
-----+-----+-----+-----+-----+-----+-----+
      1090                     1110                     1130
      .                      .                      .
ACTCCTTGGGAGAAGTCGTGTTTACAGATGGTGGGTGTCACCCATGCCAAGCACTTCTAA
-----+-----+-----+-----+-----+-----+-----+
      1150                     1170                     1190
      .                      .                      .
GGGTTAATGCTCACTGTTTGCTTGGCTTCCAGGACATTTCTGATGCCCTCTGGAGGG
-----+-----+-----+-----+-----+-----+-----+

```

FIG. 29.2

```

      1210              1230              1250
TGACGCCAACCAAGCCAGTGGAGAAGCCATCTTCCCAGGTGCTGTCAGGCGCCCCCGGAG
-----+-----+-----+-----+-----+-----+-----+
      1270              1290              1310
CTGCTCGGTGCATCCTAGGATCCCTCTTCCTCAGCTTTGGTTTGATGGCCTCATCTCCTC
-----+-----+-----+-----+-----+-----+-----+
      1330              1350              1370
CCCTGCAACCTCAAAATGTAAATAAACCCCTTCTCAGAGACTTCGGCAGAAAATTCTCT
-----+-----+-----+-----+-----+-----+-----+
      1390              1410              1430
GACCTGCACTTGGACACAGCTCATCTGGGTTTGGGAGGTGTCAACTGTGTAAGGATGACT
-----+-----+-----+-----+-----+-----+-----+
      1450              1470              1490
CTGATCCCCATGTGGCTTTTCGACTGTGTCCCTCTACAGTCAGTTATTAGCACTGACTG
-----+-----+-----+-----+-----+-----+-----+
      1510              1530              1550
TGCTAGGAAGTGAGCAACACACATATTCCCAGACCACATGGAGCTCAGGAGCTTGGGGAG
-----+-----+-----+-----+-----+-----+-----+
      1570              1590              1610
AGAGACAGGGAAGTGGACGACTACAGGGCCTTCTGAAACGTGTTGCAGGGAGAAGTGTA
-----+-----+-----+-----+-----+-----+-----+
      1630              1650              1670
GTCAGGGGATGCTAACCTGGCTTTGGGTAAGGGACAGCCTCTGAATGACAGGACATTAAA
-----+-----+-----+-----+-----+-----+-----+
      1690              1710              1730
GCCATGGCCTGCAGTTTAAGTAGGAGTTGGCCAGTTCGAGGTAAGAATACCAGTAAGCAA
-----+-----+-----+-----+-----+-----+-----+
      1750              1770              1790

```

FIG. 29.3

```

GAACGCCAGAGTAGCTCCTCGAGCTGCCTTCTGTACCTGACATCCACACTGAAGCCAGCC
-----+-----+-----+-----+-----+-----+
      1810                      1830                      1850
CCTCTGTGTTTCAGCCTTGCTTTACTGAAGAGGTGTCGCTGAGGGGCTGCTCTGGGGTGCT
-----+-----+-----+-----+-----+-----+
      1870                      1890                      1910
GCTCTGCTTTCCTGTCCCCAACTTGTTCTGAGCTCGAGCCACCTCCATACTGGTGCTCCT
-----+-----+-----+-----+-----+-----+
      1930                      1950                      1970
GGTTCCTCAGGCCTTTGAACTCAAACCTGAATCACACCACTGGCTTTCCTCGTTCTCCAGCT
-----+-----+-----+-----+-----+-----+
      1990                      2010                      2030
TGCAGATGGCAGATTCGGGAACCTTTTGGCCTCCATAATCACGTGAGCCAATTGCTATAA
-----+-----+-----+-----+-----+-----+
      2050                      2070                      2090
TAAATATCTCTCTCCCTCTTTCTCTCTCTCTCTCTCTCTGCAAATATAGTTCCAATTA
-----+-----+-----+-----+-----+-----+
      2110                      2130                      2150
TAAGAGCCCCCTAACTGGAAAAATAACCCCTATGGTGCACTGGTGAGTAGAGAAACTGTGGTT
-----+-----+-----+-----+-----+-----+
      2170                      2190                      2210
CCCTCAAACCAACCGAACACTATTTCAGCAATACGAAGGAACAAACTATTGATATGCAAAAT
-----+-----+-----+-----+-----+-----+
      2230                      2250                      2270
AGTGTAATGAATCTCAAAAACATCGGAAAGAGGGAAGGAAGCCAGACACAGAAGAGTGC
-----+-----+-----+-----+-----+-----+
      2290                      2310                      2330
ATGCCGCATGATTCATTATATGAAATCTAGAACAGGCAAAACCTATCTATAGACAGA
-----+-----+-----+-----+-----+-----+

```

FIG. 29.4



```
2350                2370                2390
GAACAACAGATCAGTGGCTGCTCTGGGGTTGGGAGTGGGGAAAGTTTGCTGGAAGGGCACA
-----+-----+-----+-----+-----+-----+-----+-----+-----+
2410                2430                2450
GGGCTCTTTCTGTGAGTGAGGGAATGTGTCTGCATTATAGTGATGCTTATGTAGTTATAT
-----+-----+-----+-----+-----+-----+-----+-----+-----+
2470                2490                2510
ACACTTATCGAAACTCATCTTACTGGCCACTTAAAATAAGTGCATTTTATTGTGTGTAAA
-----+-----+-----+-----+-----+-----+-----+-----+-----+
2530                2550                2570
TTATACCTTAATGAAGTTGATTTGAAAATCCAAAGTAGTAATAATAAGTAATAATCTCGT
-----+-----+-----+-----+-----+-----+-----+-----+-----+
2590                2610                2630
AGCTGGACAGCTGTGGTGACTCACTCCTGTAAATCCAGCGATTTGAGAAGCTGAGGCAGG
-----+-----+-----+-----+-----+-----+-----+-----+-----+
2650                2670                2690
AGGATCACTTAAGATCAGGAGTTCTTTTATTTTATTTTATTTTATTTTGGAGACGGAGTTT
-----+-----+-----+-----+-----+-----+-----+-----+-----+
2710                2730                2750
CGCTCTTGTTGCCCGAGGCTGGAGTGCAATGGCATGATCTCGGCTCGCTGCAACCTCCACC
-----+-----+-----+-----+-----+-----+-----+-----+-----+
2770                2790                2810
TTCTGAGTTCAAGCGATTTTCTGCTCAGCCTCCCAAGTAGCTGGAACCTACAGGCGCTC
-----+-----+-----+-----+-----+-----+-----+-----+-----+
2830                2850                2870
ACCACCATGCCCCGCTAATTTTGTATTTTATGTAGAGATGGGGTTTCACCATGTTGGCC
-----+-----+-----+-----+-----+-----+-----+-----+-----+
2890                2910                2930
AGACTGGTCTTGAACTCCTGACCTCCAGTGATCTGCCCGCCTCGGCCTCCCAAAGTGCTG
-----+-----+-----+-----+-----+-----+-----+-----+-----+
```

FIG. 29.5

2950                      2970                      2990  
 GGATTACAGGCATGAGACTGCGCCTGGCCAAGACCAGAGATTTGAGACCAGCCTGGGA  
 -----+-----+-----+-----+-----+-----  
                 3010                      3030                      3050  
 AACAAAGTGAGACCCCTGTCTACAGAAAAATTAAAATTTTAGCTGGGCCTGGTGCCGT  
 -----+-----+-----+-----+-----+-----  
                 3070                      3090                      3110  
 GTGCCTGTAGTTCCAGCTACTCAGGAGGCTGAGGTGGGAGGATACTTGAGCCCAGGATT  
 -----+-----+-----+-----+-----+-----  
                 3130                      3150                      3170  
 TCAAGGCTGCAATGAGGCATGATCAGGCCACTGTCTCTAGCGTGGGTGACAGAGTGAGA  
 -----+-----+-----+-----+-----+-----  
                 3190                      3210                      3230  
 CCTGTCTCTAATAATAATCATAGAACAACAAGGACCTCTAAACGCACTGATATCTA  
 -----+-----+-----+-----+-----+-----  
                 3250                      3270                      3290  
 AGGTGTATTAAAGCGACCAAAAAAAAAAAGAAAATCAAAGTCAGAAAAACGTTAATAAGA  
 -----+-----+-----+-----+-----+-----  
                 3310                      3330                      3350  
 GAAAAAATATGTCTGTATTGTCTTGAGTGTGAAAAAATAATCTAAAGCCTATGAAAG  
 -----+-----+-----+-----+-----+-----  
                 3370                      3390                      3410  
 AACTAATCATATTGTTTCCTGTTGGTGAGGAGGCTAAGAGCACGGAGACTTTTCCTTA  
 -----+-----+-----+-----+-----+-----  
                 3430                      3450                      3470  
 TGCTTTCTGTACTTTTTGATTTTGAGATATGTGAATGTAGGTTTCTCTCACTGCTCGAAC  
 -----+-----+-----+-----+-----+-----  
                 3490                      3510                      3530

**FIG. 29.6**

TTTCACTAACCAAATTACTACATTCCAATTCTCAAAAACAAATAGATTTACTTAAAAGT  
-----+-----+-----+-----+-----+-----+-----+  
3550 3570 3590  
AGGCTGGGTGCGGTGTCTCACGCCTGTAATTCAGCGCTTTGGGAGGCCGAGGCGGGCAG  
-----+-----+-----+-----+-----+-----+-----+  
3610 3630 3650  
ATCACCTGAGGTGCGGAGTTCGAGACCAGCCTGACCAACATGGAGAAACCCCATCTCTAC  
-----+-----+-----+-----+-----+-----+-----+  
3670 3690 3710  
TAAAAATACAAAATTAGCCAGGCGTGGTGGCGAATGCCTGTAATCCAGCTACTCGGGAG  
-----+-----+-----+-----+-----+-----+-----+  
3730 3750 3770  
GCTGAGGCAGAAGAATCACTTGAATCTGGGAGGCAGAGGTTGCAGTGAGCCAGATCATG  
-----+-----+-----+-----+-----+-----+-----+  
3790 3810 3830  
CCATTGCACTCCAGTCTGGGTAAACAAGAGAGAACTCTGTCTCAAAAAAAAAAAAAAAAAA  
-----+-----+-----+-----+-----+-----+-----+  
3850 3870 3890  
AAAAGATTTGCTTAAAAGTTAACATCTCCGGCCGGGCGCGGTGGCTCATGCCTGTAATCC  
-----+-----+-----+-----+-----+-----+-----+  
3910 3930 3950  
CAGCGCTTTGAGAGGCCGAGGCGGGTGGATCACGAGATCAGGAGATTGAGACCATCCTGG  
-----+-----+-----+-----+-----+-----+-----+  
3970 3990 4010  
CCAAAATGGTGAAACCTCGTCTCTGCTAAAAATACAAAAGTTAGCTGGGGGTGGTAGCGC  
-----+-----+-----+-----+-----+-----+-----+  
4030 4050 4070  
GCGCCTGTAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCGGGAGT  
-----+-----+-----+-----+-----+-----+-----+

FIG. 29.7

```

      4090              4110              4130
CGGAGGTTGCAGTGAGCCAAGATCGCGCCGCTGCACTCCAGCCTGGCGACAGAGGGAGAC
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      4150              4170              4190
TCCATCTCAAAAAAAAAAAAAAAAAAAGTTAACATCTCATCCAAATTTGCACCGAGTA
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      4210              4230              4250
GGAAAACAAAAGTTTAAAAACATGAAACAGATGTTACTGAGGCCGAAAGGGTCTCCAGGC
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      4270              4290              4310
CTGGGAGTCTGCAGCTTTTATGCAATTCTGCCCTCTGGCCACCGCCAGGGAAGAAAGGTT
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      4330              4350              4370
GTCTCCGTCTGCTGCATCGCCTTTGCCCCAGCAATGAAGCCCCCAAGACAGCGGCAGCCGG
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      4390              4410              4430
TTGCCTGAACCTTCCTATCCTTGGGGGCACCCAGTGCAGGTGGATGACCCGACTCAACCT
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      4450              4470              4490
CCGCCAGGGCACCCCTCGGGGCAGGACGGGTAGCAAGGAGGGGACAGAGATCGGCCCCAGG
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      4510              4530              4550
AGACCACGGAAGATCGCGCTCCTGGGGCCAAC TTCAGCAGCGAGAGGCGGCCTTTGCCCA
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      4570              4590              4610
CCGCCTCATCCACACGCGCGGTCTCCAAGAACCTTCCAGCGGTTCTCTCTCTCTC
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      4630              4650              4670
TCAGGAGTAGAGGCCCTCTGAGACCGACGGGGAGGGACGGCTCGGGCCGCTCATCCGAGG
-----+-----+-----+-----+-----+-----+-----+-----+-----+

```

FIG. 29.8

```

      4690              4710              4730
      .               .               .
GGCCGCACGGATTCCTTCCTCCGCCAGCTCCACCCCTCGAGGGGCGGCGGTCCGGGAG
-----+-----+-----+-----+-----+-----+-----+
      4750              4770              4790
      .               .               .
TGGCGACCCGGCTCCCCCATGGCGCGCGCCGTCGGGGCCCTGGCCAGGCTCCGAGCGGG
-----+-----+-----+-----+-----+-----+
      4810              4830              4850
      .               .               .
GTTGGCGGGGAGGGGAGGCGGGAGCGAGGCGGGCGGTGGGAGGTGGGGGCGGGAAGGTC
-----+-----+-----+-----+-----+-----+
      4870              4890              4910
      .               .               .
CGAAGGCGGCGGCTGAGGCTGCACCGGGCACGGGTCGGCCGCAATCCAGCCTGGGCGGA
-----+-----+-----+-----+-----+-----+
      4930              4950              4970
      .               .               .
GCCCGAGTTGCGAGCCGCTGCCTAGAGGCCGAGGAGCTCAGCTATGGGCTGGAGCCC
-----+-----+-----+-----+-----+-----+
      4990              5010              5030
      .               .               .
CGGAGAGCTCGGGGACCCCGTTGCTGCTGCTGCTACTACTGCTGCTGCTCTGGCCAGTG
-----+-----+-----+-----+-----+-----+
      5050              5070              5090
      .               .               .
CCAGGCGCCGGGGTGCTTCAAGGTGAGGACGCGGGCGGGGTGCGCCCTGAGGGGCAAGGCT
-----+-----+-----+-----+-----+-----+
      5110              5130              5150
      .               .               .
AGGCGCGGTGGTGGTGGCGGGATGGGTCTGCTCAGAGCTCGGGTCAGCGCGGAGGG
-----+-----+-----+-----+-----+-----+
      5170              5190              5210
      .               .               .
TCTCAGCGCCCGGCACCATACGGCCAGTAGGTCAGGGCGTGGGGACTCTTTGGGGGGGT
-----+-----+-----+-----+-----+-----+
      5230              5250              5270
      .               .               .

```

FIG. 29.9

```
CTCCGTGGGACCTGCCCAGGGACGCTCAAGTGTGCTTGGGCTGGCCCCGGGCCCGGACTT
-----+-----+-----+-----+-----+-----+-----+
      5290                      5310                      5330
GCCACACTGCCC GGCTGCCACTCCGCTGGCAAAGCAGAGGGCATGGCTCCCTCCCCCTC
-----+-----+-----+-----+-----+-----+-----+
      5350                      5370                      5390
GGGGACAGCCCAGCCCCAGCCCCAGCCCCATAGCCGTAGCCCCCTCTGCCTGGATTCTC
-----+-----+-----+-----+-----+-----+-----+
      5410                      5430                      5450
GCTCTCACAAC CAGCTTCCATCCGCAGGCCACCGTGTGACCCGCTCCTGCTCCTCCACCC
-----+-----+-----+-----+-----+-----+-----+
      5470                      5490                      5510
CTTAGGACTCAGCGGGGCTCCATCCTCTAGGAAGCCCCCATGCCCAAGAGTCCCCCAGAG
-----+-----+-----+-----+-----+-----+-----+
      5530                      5550                      5570
TCCCTGCTTTGCTCTCAGGCTGCAGAACTAGCTGTGGCCTCCACCCCTGCTCACCCCTCGT
-----+-----+-----+-----+-----+-----+-----+
      5590                      5610                      5630
CCCTCCTCCCAGGGCAGCAGGGCAGTGTGTATGTTGTTTATATTGTTGCCTTGTTTGGTG
-----+-----+-----+-----+-----+-----+-----+
      5650                      5670                      5690
AGATAGAGAAGGGCCTCTCCAGATAGAAGGTGTCTGTTTAGCAGTGTCTTGAAAGACTG
-----+-----+-----+-----+-----+-----+-----+
      5710                      5730                      5750
CAGCTGTCTCCTCGGGGTAACCCCTCCAAACAAAGATGTTAAGATGGGGCTGGAACAACC
-----+-----+-----+-----+-----+-----+-----+
      5770                      5790                      5810
TCTGCAAGCGGGTGGGAGGATTAGCCAGTCCTGCACAGCAAGTCCTGGCCGGGAACAGG
-----+-----+-----+-----+-----+-----+-----+
```

FIG. 29.10

```

      5830                      5850                      5870
GAGGGCAACCAGGGAGGGGGCATGCGGGGCTGGGCTGTGCTATGCAGACTGGGCGGTGGC
-----+-----+-----+-----+-----+-----+-----+-----+

      5890                      5910                      5930
TTCCACAGCACTGTGTGGGGACCAAACAGGTACAGGGGCTGGTCTGTCTTGGCCCCAGG
-----+-----+-----+-----+-----+-----+-----+-----+

      5950                      5970                      5990
GGAGGGCCCCAGGCGGTCCACTGCTCCCTCCCTCTGAGCCCTATCCTGGGGGTCAGGGGA
-----+-----+-----+-----+-----+-----+-----+-----+

      6010                      6030                      6050
GGTGATGGGACCCCTGGGAGAGGGGCGTCTATGTGCCCAATACCAGCCTGGCTCCCTCGG
-----+-----+-----+-----+-----+-----+-----+-----+

      6070                      6090                      6110
GTTCCACCCCCATTACCCCGGTACCCGGAGCTCCAGCTCCAGCTCCAGCTCTGCCCTCT
-----+-----+-----+-----+-----+-----+-----+-----+

      6130                      6150                      6170
CTCCCTCATTTGGGGTCAGGGTGCCCGTGGCCAGCACGTGCGCGCAAGGCCATGTGGACAG
-----+-----+-----+-----+-----+-----+-----+-----+

      6190                      6210                      6230
CACCCACACACCACACTGCACCCACACCACACCTGTGCCCCGGGCCACCTACCTCTTCC
-----+-----+-----+-----+-----+-----+-----+-----+

      6250                      6270                      6290
CCAAACCCCTTAGAGGCCTAGGAGCAGCAAAGCTTGGTTCTCTACTCTCAGTTAAGTGCTC
-----+-----+-----+-----+-----+-----+-----+-----+

      6310                      6330                      6350
TCTGGGCTGAGAGACCTCCCTCCTTCCCTCCCTCCCCACATCCACTCAGAGCCCTCCCTGC
-----+-----+-----+-----+-----+-----+-----+-----+

      6370                      6390                      6410
ACTGGCCCCCTCTAGCCTCCTTTCCAAAGGTGGCAGACTCCTCTCGGCCCTCATCTGCCTGA
-----+-----+-----+-----+-----+-----+-----+-----+

```

FIG. 29.11

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6430	6450	6470
TGGCAATTCACTCATCCAATCAAGGAGGGCTTCTTGAGGAAGGGCTTTGTATGTTTGTATA-----+-----+-----+-----+-----+		
6490	6510	6530
GTCCTGGGACAGAAAGGTGGAGGAGAAAAAAGGAGTTGGCGTGGCCTAGCAGGAGCTGAGTCTC-----+-----+-----+-----+-----+		
6550	6570	6590
ACTTCCACAGGCAGCCATCAGCCCAGCAGGACTGAGGCCAGGGCTGCGTGGAGGGGGGAG-----+-----+-----+-----+-----+		
6610	6630	6650
GCTGTCTGTCTCTGGGAGCTGGGACTGGGSTACCGGGGAAGGAGGGCTGCTGCAGGCTCTG-----+-----+-----+-----+-----+		
6670	6690	6710
GGTGCTTGSGGCTTGGCTCCTGCAGGGCGGGCCTGTGAGAGTGGTTGGGGCCAGTGGAGG-----+-----+-----+-----+-----+		
6730	6750	6770
GGCTGGGAGCATTCCAGGGGAACATTCCAGGCGCCCTCTGAGTAATGCTTGGCTCTGGGAA-----+-----+-----+-----+-----+		
6790	6810	6830
TTCTCTCTTAGAGCCCCCTTAGGCACACCCGGCCAGGGAGCACCAAGGCTCCGTCCGGAAG-----+-----+-----+-----+-----+		
6850	6870	6890
CGTCCCTCTCCCTTGAAGAGATGAGGAGGGGCCCTTCTGGGCCAGGGTACCACAAAACCTGCTC-----+-----+-----+-----+-----+		
6910	6930	6950
CACCAGGACAGAGTCCCCGAGGGAGCTCTGGGCAAGGTGGACCTCGCAAGGCAACATCTG-----+-----+-----+-----+-----+		
6970	6990	7010

**FIG. 29.12**



GCTGTTGTTTTTCTCAGATGATGGGGGGGCACAAGTGTCTCTCTTCGTACATCTCTCA  
-----+-----+-----+-----+-----+-----+-----+  
7030 7050 7070  
CCCTAAAGGCATCTGCTGCCCATCTAAAAATCCCTAAGGCTGCCGCGCTCTTTCCTTCCC  
-----+-----+-----+-----+-----+-----+-----+  
7090 7110 7130  
CTCTGCACTGGCGGCCTTGGCCTCTTCCTTGTGATCGCCGAGCCCAAGCCTGCCCCCGA  
-----+-----+-----+-----+-----+-----+-----+  
7150 7170 7190  
CAAAGGTCAGGGGACTCCCGTGTCCCCAGCTGAGCTGTCCCTTCCAGCCTTCTCTTTT  
-----+-----+-----+-----+-----+-----+-----+  
7210 7230 7250  
CTCTCTCTTGATAGCTCCTCAGATCCAAGGATGCCACGGGCGTCCCTCCTTCTCCAGGC  
-----+-----+-----+-----+-----+-----+-----+  
7270 7290 7310  
TGAGCCCACGCGTGTGAAGGTGAAGTCTGCCCCAAAAGGCCTCCAGTGCCTCCCTGGGG  
-----+-----+-----+-----+-----+-----+-----+  
7330 7350 7370  
ATGTCCTCTACCCCCCTCCCTCTGCTTTGTCCCATGCCCCGTGTGTTCCTCAGGTCCCCCT  
-----+-----+-----+-----+-----+-----+-----+  
7390 7410 7430  
CACCTGTGCTCTGTCTTTACTCCAGGACATATCCCTGGGCAGCCAGTCACCCGCACTG  
-----+-----+-----+-----+-----+-----+-----+  
7450 7470 7490  
GGTCCTGGATGGACAACCCTGGCGCACCGTCAGCCTGGAGGAGCCGGTCAGTGCCATGTC  
-----+-----+-----+-----+-----+-----+-----+  
7510 7530 7550  
TCCCCGCCCTCCACAGGGGCCCTGAACCTCCCAGCCCTTTTGTCTCTCCCTACATTACAG  
-----+-----+-----+-----+-----+-----+-----+

FIG. 29.13

```

      7570              7590              7610
      .               .               .
CTTCTAGTTTGTGCTGGGGTCCCCAGAACCACCAAGTCACTACTCCTATAGGCCCTGCCT
-----+-----+-----+-----+-----+-----+-----+
      7630              7650              7670
      .               .               .
CCCCTGCCCTCAAGTGGGCAGAAGAAGGCACTGGGGTTTGGACATCTGGATCTCGTGAG
-----+-----+-----+-----+-----+-----+
      7690              7710              7730
      .               .               .
CCCGCACACATGGAAGTCATTTTCAGCTTTCACCCCCACCTCCCTCTTCCCTCCCTCC
-----+-----+-----+-----+-----+-----+
      7750              7770              7790
      .               .               .
CTGGATGATCTGGGCCACCCCCACCCCCACCAGGCAGAAATGGGTCCAGAGTTTGTGGGT
-----+-----+-----+-----+-----+-----+
      7810              7830              7850
      .               .               .
CCTGAAGCTTTTCAGGAGCCTCTAAAAAAGCAAGCAAGCAAGCAAGCAAGCAAGCAAG
-----+-----+-----+-----+-----+-----+
      7870              7890              7910
      .               .               .
CCTTTTGCAAAGTTGACCAAGACATGTGACCTGTGGACACACTGCTGTCCCTCTCAGGG
-----+-----+-----+-----+-----+-----+
      7930              7950              7970
      .               .               .
CCCTGCCACGAAGGCCCTGAACCTTCAGCCTCACTGGCTCCTGTGGAATCCACTTCTGGTA
-----+-----+-----+-----+-----+-----+
      7990              8010              8030
      .               .               .
TGGGGGGGGCAGTGGTCACTCTCTGATGTCCCCCAGATGTAAGACCACCCCATGTGCTT
-----+-----+-----+-----+-----+-----+
      8050              8070              8090
      .               .               .
CTTCTGCAGGACGCTCTGCCCCAGCCTCTTCCCAATCCCGCTCTTCACACGCTTCCAGAA
-----+-----+-----+-----+-----+-----+
      8110              8130              8150
      .               .               .
TAACCATGCCCATCTGTTTGTGCCATAATATCTGTGCTGCAAACCTAAGAGGGCAGTAGC

```

FIG. 29.14

-----+-----+-----+-----+-----+-----+  
8170 8190 8210  
CTTGATATGCTCATTTTACAGAGGGGCAAACGGAAGCCCAGAGAGCTTGGGGAAATTGTC  
-----+-----+-----+-----+-----+-----+  
8230 8250 8270  
CATGGTCACACAGCTCTTTAGGCTGGGAGCCTGAGACCCACTAAGGTCTGAACGATTTTA  
-----+-----+-----+-----+-----+-----+  
8290 8310 8330  
AACCATTGGCTACACCCCTGCCCTCCTAGAGAGCCCTCTTTGTTGGAATTTTCAGCCC  
-----+-----+-----+-----+-----+-----+  
8350 8370 8390  
TACTGTCCAAATCCAGCAAGAGGGAAGGCAGGGGAGCATTGCCATGAAGGCTGAGAGGCC  
-----+-----+-----+-----+-----+-----+  
8410 8430 8450  
CCCAGAGACCCAGCAGCTCCCAACCCAGGGCCCTCACTGGGATCCCCTAGGCCCATTAAGG  
-----+-----+-----+-----+-----+-----+  
8470 8490 8510  
CCCCCATTCCTACTGGTCAAGCACGGCACTGGCCTGAGCTTTGAGATTGCCCTCCCCATCC  
-----+-----+-----+-----+-----+-----+  
8530 8550 8570  
CCAGGAGGGGAAGGCTGGACACACACTGGGGTCACTCTGCCTCTGGGCCTCCCTGTCTGT  
-----+-----+-----+-----+-----+-----+  
8590 8610 8630  
CTGGCCTGGGCTGTGACCAAGAGGAGAGCCCCAAAGGGGCTCTGCTTCCCCCACC GGTTGG  
-----+-----+-----+-----+-----+-----+  
8650 8670 8690  
GCCCCCTGCCCCAGGAAGCCTGCCAAGATGGTACAGAAGAAAGAGTAGAGGCTAGGTATC  
-----+-----+-----+-----+-----+-----+  
8710 8730 8750

FIG. 29.15

CCCTCCAAAAGGCAGGAAACACTCACATTTCAAGATGAGGGGTATATATCAAGGGGCAGG  
-----+-----+-----+-----+-----+-----+-----+-----+-----+  
8770 8790 8810  
GTACCAGGAGGGCAAGAGTAAAGATAGCAGGGGCTGCAGAGGAACAGGGACCTCGAGTAT  
-----+-----+-----+-----+-----+-----+-----+-----+-----+  
8830 8850 8870  
GGCCTTTTCCCGGTGCAGACCTTCCCCAATAAAGCAAGTGGCATTCCAGCCTCATGAG  
-----+-----+-----+-----+-----+-----+-----+-----+-----+  
8890 8910 8930  
CTCATGCTGGAGGCCCTTGTGGGGCCTGTGGCCAGGGAGGCAAGGACCATCTGCTCCCCAC  
-----+-----+-----+-----+-----+-----+-----+-----+-----+  
8950 8970 8990  
TTGCGAAGGAAGAACTCCCTCCAAAGACTCTGAGACCCCTTGGACAGGGCCCCAGGCCAGT  
-----+-----+-----+-----+-----+-----+-----+-----+-----+  
9010 9030 9050  
GCATTTTGGAGAAAAGGAGTTCGGGGTTAAACATTCCGAAGGCGCAGCAGCCTCCCAGG  
-----+-----+-----+-----+-----+-----+-----+-----+-----+  
9070 9090 9110  
AAGCTCCTGGGCCGGCTCCAACCTCTGGGCCCCAGCCAGGCTGAGTGGACAAGGGGGAAG  
-----+-----+-----+-----+-----+-----+-----+-----+-----+  
9130 9150 9170  
TGGGGTGTTCACAGGGTGGGAGACGCCAAGAGGGTGGGGGAAGGAGAGAGGGGTGGCC  
-----+-----+-----+-----+-----+-----+-----+-----+-----+  
9190 9210 9230  
GTCCAAGCCAGCCTCCTGACACCTAGCTGAGAGCCAGTGTGCTCTCTTGGCTGGAATGGC  
-----+-----+-----+-----+-----+-----+-----+-----+-----+  
9250 9270 9290  
GTCCATGTTTACTTCGTGGGTCCAGTGAAGCAGGTGTGCGAGCCGGAGGGGACGGGGGCTG  
-----+-----+-----+-----+-----+-----+-----+-----+-----+

FIG. 29.16

```
          9310                9330                9350
CTGGAGGCCACGAAAACCTTGAAGAGGGAGCAGTTTGCCAAATGGAAAGTGGAGGAG
-----+-----+-----+-----+-----+-----+-----+-----+-----+

          9370                9390                9410
TCAAATTTGAATTCTATAGGAAATGAGCAGCAGCTCATTGGAACCAAGCCTCAGGTAGC
-----+-----+-----+-----+-----+-----+-----+-----+-----+

          9430                9450                9470
AGAGGCTCTGAGGAGGCCCTGACCATGGCTACCCGATGCCCCATAATGTCCTCAGCACCC
-----+-----+-----+-----+-----+-----+-----+-----+-----+

          9490                9510                9530
CCTCTGTCTTCCCCCTGCTTTTGATGCCCTTCTGGGCATGAAAGAAGAGGGCGGGGCCAG
-----+-----+-----+-----+-----+-----+-----+-----+-----+

          9550                9570                9590
GGGAGGGGCACCTTTCTGGGACCTCTGGTCTCTAGGGAGGATGCTGGTGTGCCTGGCAGG
-----+-----+-----+-----+-----+-----+-----+-----+-----+

          9610                9630                9650
CTGTGCCAACGCCCTTCCAAGTGGCTGTTGTTCAGGACTGCAAACATCCTGAGTTTGGGAA
-----+-----+-----+-----+-----+-----+-----+-----+-----+

          9670                9690                9710
CATCTTTGTATGTTCTCACCTCCTCCACGCCCTCCATAGTATGTGGGGGGTCTGTCTGAC
-----+-----+-----+-----+-----+-----+-----+-----+-----+

          9730                9750                9770
TCCCCAGCCCACGTTCTCCCAAGAACTTCTCCCCAGCCGGCTCCACAGGCCACCTACT
-----+-----+-----+-----+-----+-----+-----+-----+-----+

          9790                9810                9830
CCCTGGCAGGCAGGAGGCCTGGAGGCCACCATCTCAGCTCCACACTCTTTCTTGCCCAGG
-----+-----+-----+-----+-----+-----+-----+-----+-----+

          9850                9870                9890
TCTCGAAGCCAGACATGGGCTGGTGGCCCTGGAGGCTGAAGGCCAGGAGCTCCTGCTTG
```

FIG. 29.17

```
-----+-----+-----+-----+-----+
          9910                9930                9950
AGCTGGAGAAAGAACCAGTGAAGTCCAGGCTGGGGTAGGGCTGGGAGGAGGGGATCAGTGT
-----+-----+-----+-----+-----+

          9970                9990                10010
TGGGGGGCAGGGACTGACACAGATCTGTGCGGGTGGCTGGATGGGCAGAGGACCCAGAG
-----+-----+-----+-----+-----+

        10030                10050                10070
AGGGTGCAGATGACAGGGAGAGTCAAGCAGGCCTGTGGTGGCTCCCTGGAGGCTGAAGA
-----+-----+-----+-----+-----+

        10090                10110                10130
GGACCGCTGAGGCTGTGAGCCCCGCTGTGGGGCACCTCCGCCCTCCCAACCCAGGAGCG
-----+-----+-----+-----+-----+

        10150                10170                10190
GCTTGTTAGCTCCCTGCTGGCGATGAGTGAGCACCACTAGTGGACATTGCAAGATATG
-----+-----+-----+-----+-----+

        10210                10230                10250
CTGAGTCTAAAGAAATCCTAGAGGGAAAAGATGAGCCGGCACCCAGGCTAAGGGAAATGG
-----+-----+-----+-----+-----+

        10270                10290                10310
CAGGGACCAAGATGCGGTGGCTTTGGGAGGCCGAGGCGGGCGGCTCACTGAGGTGAGGA
-----+-----+-----+-----+-----+

        10330                10350                10370
GTTTGAGACCAGCCTTGCCAAACATGGTGAAACCCCGTCTCTACTAAAAATACAAAAAAT
-----+-----+-----+-----+-----+

        10390                10410                10430
AGCCAGGCGTGGTGGCGGCGCTGTAATCCAGCTACTTAGGGGGCTGAGACGGGAGAAAT
-----+-----+-----+-----+-----+

        10450                10470                10490
```

FIG. 29.18

```
CGCTTGAACCCCGGAGGTAGAGGTTGTGGTGAGCCAAGATCACACCACTGCACCACTCCG
-----+-----+-----+-----+-----+-----+-----+
10510              10530              10550
GCCTGGGCAAAGAGTGAGACTCCGTCTCAAAAAAGAGAAAAAGAAAAAGAAAAA
-----+-----+-----+-----+-----+-----+
10570              10590              10610
AAAAGAAAGAAAAAGAAAAAGATGCAGTGGCTACACTTGGGGGCAGCAGTTTGT
-----+-----+-----+-----+-----+-----+
10630              10650              10670
CTGACCTGCCTGGAAGGCTCTCCATCTACAGGGAGGGGAGCAGGGGGGAATGAATTGGAG
-----+-----+-----+-----+-----+-----+
10690              10710              10730
AGTCCCAGGAGGGCCAGATCACAGAAGGCCATTTTGGTGCTCAGTGTCTCGGACCATCCA
-----+-----+-----+-----+-----+-----+
10750              10770              10790
GAGCCAAAGATTTTGAGCTGGGGGAAGGGACAGGCAGACCTGTGCTCAGGAAGGTGCCTTG
-----+-----+-----+-----+-----+-----+
10810              10830              10850
GGCTGGGTGGGGTGGGTGTCCGGGCTGGAGCGCAGGCTCTTAAACCACCCAGATTATGT
-----+-----+-----+-----+-----+-----+
10870              10890              10910
TATCAGTATATATCACCTACTGAGTGTCTGACCGCAGGCGCTGTCTGAGCACTTGACAC
-----+-----+-----+-----+-----+-----+
10930              10950              10970
GTATTTTATTCTCCCTCGTGGAGTCGGATGGACAGGGAACAACTCTAGTTCCACTGTGC
-----+-----+-----+-----+-----+-----+
10990              11010              11030
CCAACCATATTTTCCGACGTCCCTACCCCTTCAATGGGGTGGTCACATCACCTACCTCC
-----+-----+-----+-----+-----+-----+
```

FIG. 29.19

```
11050      11070      11090
TAGGGTGGCGGGTGTGTGTGGGGCAGGGGTAGGGGGCAGAGCTGGGGCAGGTGGTGAAT
-----+-----+-----+-----+-----+-----+-----+

11110      11130      11150
GCCTGGGAGGGGGGAAGCAGCCATCATTAGCGGGTGGTCTGGAGGTAATGAGGCCAAGGT
-----+-----+-----+-----+-----+-----+-----+

11170      11190      11210
GAGGTTGGGTTAAGGATTTTCTTTAAAGAAGACAGATTGACTTATGATTGATCCATCCGT
-----+-----+-----+-----+-----+-----+-----+

11230      11250      11270
GTGGGAAGATCCTGTTGAGATGGAGCCTGAAGATGGAATCATTACCGAGTGGGTGTGG
-----+-----+-----+-----+-----+-----+-----+

11290      11310      11330
AGAAGGCAGGGAGGGTGGGAAGCAGCGTGGGCAGGTGGCGATTCTGTTTCTCTGGAGGCA
-----+-----+-----+-----+-----+-----+-----+

11350      11370      11390
GGGGGTGAGCATCAATCACTGAAGGACAGGTGGGAGGTATGTGGGGTCTAGAAGTCTGAG
-----+-----+-----+-----+-----+-----+-----+

11410      11430      11450
GAAATATTTCAAGGATCTAGGCGAGGTGGGGGCAAGAGGGTCGACCAGATGCCCCAACA
-----+-----+-----+-----+-----+-----+-----+

11470      11490      11510
AGGAGGGCAGCAGGCAGGGAACTGGGGGAGGTACCCGCATTTCCCCAACTCCAAGTCCC
-----+-----+-----+-----+-----+-----+-----+

11530      11550      11570
ATTCTTCGGCAGTGCTCTCCTGACTCCTCCCCTCCCGATCCTGTGGATCCTGCTGCCTGCT
-----+-----+-----+-----+-----+-----+-----+

11590      11610      11630
GCAGGTCCCCTGGGAACCACAAACTCTTCCCCTATTCCCACCTCCTCCCGGCGTCTCCC
```

FIG. 29.20



```
-----+-----+-----+-----+-----+-----+
      11650              11670              11690
TGGTGCCTTCCCATATTACATCTCCCACTAAGCCATCACCAAGGCTCCTTCCTCTAG
-----+-----+-----+-----+-----+-----+

      11710              11730              11750
CCCCAAGAGTTTCTGATCTGAGCAAGTCACCATGCTCCTGTCCCTTCCCTAAGACACAC
-----+-----+-----+-----+-----+-----+

      11770              11790              11810
TGTGAGTGTCTCACTCATAAAGCTGCTCCATTAGCATTTAGGGAGGAAGGCTGGGAGACA
-----+-----+-----+-----+-----+-----+

      11830              11850              11870
TCCTGGAGGAGGCAGGAGGAAGCTGAATTCAGTGTTCCCTGTAAACACCCCTCTCAGCAG
-----+-----+-----+-----+-----+-----+

      11890              11910              11930
GCTGCTGGCCCCAGGATACATAGAAACCCACTACGGCCCGAGATGGGCAGCCAGTGCTGCT
-----+-----+-----+-----+-----+-----+

      11950              11970              11990
GGCCCCCAACCCACACGGTGAGATGCTTCCATGGGCTCTGGGATGCACCGCCAGAGGTACC
-----+-----+-----+-----+-----+-----+

      12010              12030              12050
CCCCCACCATTCTCTACCCCTACTCCTCCTTGCATTCTTAAGGGGCGGTGGAGCCAGCCC
-----+-----+-----+-----+-----+-----+

      12070              12090              12110
CTACCACACCCCTCCCTCTTGGCCCTCTTGCTCCAGCCCTGGCTGAGATTGGGGCTGGCC
-----+-----+-----+-----+-----+-----+

      12130              12150              12170
CCTTCCTCCCTAGGATCATTGCCACTACCAAGGGCGAGTAAGGGGCTTCCCGACTCCTG
-----+-----+-----+-----+-----+-----+

      12190              12210              12230
```

FIG. 29.21

```

GGTAGTCCTCTGCACCTGCTCTGGGATGAGGTGAGCTCTGGGAGAGGAGGGCTGGGCCTGG
-----+-----+-----+-----+-----+-----+
12250              12270              12290
GATGGGGAAAGAGCTCCCTCACACCCGCTCCTACCCCTCTGCACCCCTAGTGGCCTGATCA
-----+-----+-----+-----+-----+-----+
12310              12330              12350
CCCTCAGCAGGAATGCCAGCTATTATCTGCGTCCCTGGCCACCCCGGGCTCCAAGGACT
-----+-----+-----+-----+-----+-----+
12370              12390              12410
TCTCAACCACGAGATCTTTTCGGATGGAGCAGCTGCTCACCTGGAAAGGAACCTGTGGCC
-----+-----+-----+-----+-----+-----+
12430              12450              12470
ACAGGGATCCTGGGAACAAAGCGGGCATGACCAGCCTTCTTGGTGGTCCCCAGAGCAGGG
-----+-----+-----+-----+-----+-----+
12490              12510              12530
TCAGGGGCATCGATCGGATGGGAGTGGGAATGCTGTATCTATAGCCCTCCAAATCAGAAG
-----+-----+-----+-----+-----+-----+
12550              12570              12590
AGACAAGGAATTACAGGCCTCGAGTCCCAGTATTTTATTGAAGTCTGAAGAAACAGTT
-----+-----+-----+-----+-----+-----+
12610              12630              12650
CCAGAAAACATGTTAAACTTCCTTCTGGGAGCTGGGGTTGGGGGTTCAGGGCTCAAGCCCA
-----+-----+-----+-----+-----+-----+
12670              12690              12710
GCAGCTTCCACTCAGGGTCCCATTTGCACCTCCGCAGGGCAGGCAGAGAAGCGCGCAGGA
-----+-----+-----+-----+-----+-----+
12730              12750              12770
CCCGGAAGTACCTGGAAGTGTACATTGTGGCAGACCACACCTGGTGAGGAGAGACCCCA
-----+-----+-----+-----+-----+-----+

```

FIG. 29.22

```
12790          12810          12830
GGGGTTGGCGGGGTCAGGGATGGGGCCAGCTCAGCCCCCTCAAGCCACCGGGATTCTCGCC
-----+-----+-----+-----+-----+-----+-----+

12850          12870          12890
TTCCCACTTCTTGACTCGGCACCGAAACTTGAACCACACCAAACAGCGTCTCCTGGAAGT
-----+-----+-----+-----+-----+-----+-----+

12910          12930          12950
CGCCAACTACGTGGACCAGGTTGGGGGCGGCGGGGAGAGAGCGGTGATGGGGGTGGCGGC
-----+-----+-----+-----+-----+-----+-----+

12970          12990          13010
GGCAGGACAGGCAGGTGCTGGTGGGGTTTGGGGAAGAGGAAGGGCGCCCCACGAAGGACC
-----+-----+-----+-----+-----+-----+-----+

13030          13050          13070
ACCGGCGCGATGGGGCGCCTGTCTCCGGCTTCAGCCCCGCTCGCCTCAGCTTCTCAGG
-----+-----+-----+-----+-----+-----+-----+

13090          13110          13130
ACTCTGGACATTCAGGTGGCGCTGACCGGCCTGGAGGTGTGGACCGAGCGGGACCGCAGC
-----+-----+-----+-----+-----+-----+-----+

13150          13170          13190
CGCGTCACGCAGGACGCCAACGCCACGCTCTGGGCCTTCCTGCAGTGGCGCCGGGGGCTG
-----+-----+-----+-----+-----+-----+-----+

13210          13230          13250
TGGGCGCAGCGGCCCCACGACTCCGCGCAGCTGCTCACGTGGGTGCCTCTGACCCGGACG
-----+-----+-----+-----+-----+-----+-----+

13270          13290          13310
CGGGTCCCGGGTGGGGCGGCCTCACCTCCCGGCCCGCCTGGTACGCGCGCGCTCCGCC
-----+-----+-----+-----+-----+-----+-----+

13330          13350          13370
CCAGGGGCCGCGCCTTCCAGGGCGCCACAGTGGGCCTGGCGCCCGCTCGAGGGCATGTGCC
```

FIG. 29.23

```
-----+-----+-----+-----+-----+-----+
      13390              13410              13430
GCGCCCGAGAGCTCGGGAGGCGTGAGCACGGTGAGCCCCCGGGCGGGGGCGAGGGAGAGA
-----+-----+-----+-----+-----+-----+

      13450              13470              13490
CAGGAGGCTCTACGGCCGCAGTGACCGCCCTCCACGGCCCCCAGGACCACTCGGAGCT
-----+-----+-----+-----+-----+-----+

      13510              13530              13550
CCCCATCGGCGCCGCAGCCACCATGGCCCATGAGATCGGCCACAGCCTCGGCCTCAGCCA
-----+-----+-----+-----+-----+-----+

      13570              13590              13610
CGACCCCGACGGCTGCTGCGTGGAGGCTGCGGCCGAGTCCGGAGGCTGCGTCATGGCTGC
-----+-----+-----+-----+-----+-----+

      13630              13650              13670
GGCCACCGGCTACGCGGGTGCGGGGCTCGGGGCTGCGGCCGGGCGGGCTAGTCTGGGACT
-----+-----+-----+-----+-----+-----+

      13690              13710              13730
TCCTCCGCTGCGTTTCTTTGGTCGTCCTCAGTTTCTCTTCTGTAAATGGGGATAATG
-----+-----+-----+-----+-----+-----+

      13750              13770              13790
ATCATAGTGTCCGCTTCAGGGTGGTTTATGAGGCTTAAAGGGAAGAAGCTCAGGCAAAGT
-----+-----+-----+-----+-----+-----+

      13810              13830              13850
GGATTCTCAACGGTATGAAGATTATTTCCGAGTAACCTGGCGAGGTTACTCCTACACCG
-----+-----+-----+-----+-----+-----+

      13870              13890              13910
GGAGGAGCACCGTCGGGTGCGGATTCCACCTTGGGTCCCGGGCTGCTCACTATTGGGGCC
-----+-----+-----+-----+-----+-----+

      13930              13950              13970
```

FIG. 29.24

GCATCGTCCCCTGTCCCGCTTGTTGTTGTGTGACTTTGCGCGGGTTACTTCCTCCTCTCTGGGC  
-----+-----+-----+-----+-----+-----+-----+-----  
  
13990                      14010                      14030  
  
TCTGCGCGTCTGCGCGCTGTAGCCAAGCCAGGGGTGGGGATCAGAGAAGCGCGGGGGTT  
-----+-----+-----+-----+-----+-----+-----+-----  
  
14050                      14070                      14090  
  
GGGGGACTGTCCCTCCATGCCCAATGCCCTCCCCGTGCCGTAGGCACCCGTTTCCGCGC  
-----+-----+-----+-----+-----+-----+-----+-----  
  
14110                      14130                      14150  
  
GTGTTTAGCGCCTGCAGCCGCCGCCAGCTGCGCGCTTCTTCCGAAGGGGGCGCGCT  
-----+-----+-----+-----+-----+-----+-----+-----  
  
14170                      14190                      14210  
  
TGCTCTCCAATGCCCGGACCCCGGACTCCCGGTGCCGCCGCGCTCTGCGGAACGGC  
-----+-----+-----+-----+-----+-----+-----+-----  
  
14230                      14250                      14270  
  
TTCGTGGAAGCGGCGAGGAGTGTGACTGCGGCCCTGGCCAGGTTAAGTCGGCTCGCCCG  
-----+-----+-----+-----+-----+-----+-----+-----  
  
14290                      14310                      14330  
  
GCCCCCACTTGCCCTCTCCGCTCAGGTCTGGGGCGCTGCGCCCTCACCTGGGCCCTTCTT  
-----+-----+-----+-----+-----+-----+-----+-----  
  
14350                      14370                      14390  
  
GCCTTCTTGGTCCCAGGAGTGCCGCGACCTCTGCTGCTTTGCTCACAACTGCTCGTCCG  
-----+-----+-----+-----+-----+-----+-----+-----  
  
14410                      14430                      14450  
  
CCCGGGGGCCCACTGCGCCACGGGGACTGCTGCGTGCCTGCCTGGTGAGGGCATGGAA  
-----+-----+-----+-----+-----+-----+-----+-----  
  
14470                      14490                      14510  
  
GGTTCAGGGTGAGGGTTTCGGGGAGCTTGGGAGCCGGCCTGTTGGCCTTAGTTAATTGGT

**FIG. 29.25**

```
      14530              14550              14570
      .                .                .
GCCCTCAGGTTCCCCCGTTGGGTGCTGGGCTTGGGTAGGCCTGGCTCCCCCAGCTCCGAG
-----+-----+-----+-----+-----+-----+-----+

      14590              14610              14630
      .                .                .
CCGCGCTCTCGGCATGGACCTCTCACTGCACGTGGCCTCTCTCTGCCTTCCCCACCACCC
-----+-----+-----+-----+-----+-----+-----+

      14650              14670              14690
      .                .                .
GTCACCTGCGCAGCTGAAGCCGGCTGGAGCGCTGTGCCGCCAGGCCATGGGTGACTGTGA
-----+-----+-----+-----+-----+-----+-----+

      14710              14730              14750
      .                .                .
CCTCCCTGAGTTTTCACGGGCACCTCCTCCCACTGTCCCCCAGACGTTTACCTACTGGA
-----+-----+-----+-----+-----+-----+-----+

      14770              14790              14810
      .                .                .
CGGCTCACCCCTGTGCCAGGGGCAGTGGCTACTGCTGGGATGGCGCATGTCCCACGCTGGA
-----+-----+-----+-----+-----+-----+-----+

      14830              14850              14870
      .                .                .
GCAGCAGTGCCAGCAGCTCTGGGGGCCCTGGTGAGAGGACACGAGCACCCCTTGACCCCTGC
-----+-----+-----+-----+-----+-----+-----+

      14890              14910              14930
      .                .                .
CCCCCATCCTCTGGTGGGGCCAGTTTCTACTGTGGGGAAGATGGGCAGGGGAAACTGAG
-----+-----+-----+-----+-----+-----+-----+

      14950              14970              14990
      .                .                .
GCCGCTGAGCGCAGCCCCCTCTCCGAGCTGCCCCCAGCCTGGCCCATGCTTCCTCAGGCT
-----+-----+-----+-----+-----+-----+-----+

      15010              15030              15050
      .                .                .
CCCACCCAGCTCCCGAGGCCTGTTTCCAGGTGGTGAACCTGCGGGAGATGCTCATGGAA
-----+-----+-----+-----+-----+-----+-----+

      15070              15090              15110
      .                .                .
ACTGCGGCCAGGACAGCGAGGGCCACTTCCTGCCCTGTGCAGGGAGGTAGGGAGTGGAGC
```

FIG. 29.26

-----+-----+-----+-----+-----+-----+-----+  
15130 15150 15170  
TGAGTGGAGGGAGCAGAAGCTATGGAGTGGGTTTGGGGAAGGGGGTACTGCAGCTGTG  
-----+-----+-----+-----+-----+-----+-----+  
15190 15210 15230  
ACCCCCCTCTACTTCCCTCCCCAGGGATGCCCTGTGTGGGAAGCTGCAGTGCCAGGGTGA  
-----+-----+-----+-----+-----+-----+-----+  
15250 15270 15290  
AAGCCCAGCCTGCTCGCACCGCACATGGTGCCAGTGGACTCTACCGTTACCTAGATGGC  
-----+-----+-----+-----+-----+-----+-----+  
15310 15330 15350  
CAGGAAGTGACTTGTCTGGGGAGCCTTGGCACCTCCCAGTGCCAGCTGGACCTGCTTGGC  
-----+-----+-----+-----+-----+-----+-----+  
15370 15390 15410  
CTGGGCTGTGGTAGAGCCAGGCACCCAGTGTGGACCTAGAATGGTGAGCTCTGCCCCACCCG  
-----+-----+-----+-----+-----+-----+-----+  
15430 15450 15470  
ACCCCTCCTTGCCGTTTGAATCCCGCAGGCCAGTGTCCCCCTCACTGCCTGGTGCACTGC  
-----+-----+-----+-----+-----+-----+-----+  
15490 15510 15530  
CCGTAGGTGTGCCAGAGCAGGCGCTGCAGGAAGAATGCCTTCCAGGAGCTTCAGCGCTGC  
-----+-----+-----+-----+-----+-----+-----+  
15550 15570 15590  
CTGACTGCCTGCCACAGCCACGGGGTGAGAGCCCGAGGAGTGGGGGTGACCTTGSGGGTTC  
-----+-----+-----+-----+-----+-----+-----+  
15610 15630 15650  
CTAATCCTACGTGACCCCTCCTCTCTCTCTCTGCAATAGCAACCATAACTG  
-----+-----+-----+-----+-----+-----+-----+

FIG. 29.27

15670                      15690                      15710  
 CCACTGTGCTCCAGGCTGGGCTCCACCCTTCTGTGACAAGCCAGGCTTTGGTGGCAGCAT  
 -----+-----+-----+-----+-----+  
                         15730                      15750                      15770  
 GGACAGTGGGCCCTGTGCAGGCTGAAAGTATGCCAGTGGGGGGCATGTGGGCAGGAGCTGG  
 -----+-----+-----+-----+-----+  
                         15790                      15810                      15830  
 GGTGGTGCACCTGCTCAGGACTCAGCGCCCCCTTCCCCCAATCCCCGCAGACCATGACACC  
 -----+-----+-----+-----+-----+  
                         15850                      15870                      15890  
 TTCTGTCTGGCCATGCTCCTCAGCGTCCTGTGCTGCCTCTGTCTCCCAGGGGCCCGCTGGCC  
 -----+-----+-----+-----+-----+  
                         15910                      15930                      15950  
 TGGTGTGTGCTACCGACTCCCAGGAGCCCATCTGCAGCGATGCAGCTGGGGCTGCAGAAGG  
 -----+-----+-----+-----+-----+  
                         15970                      15990                      16010  
 GACCTTGCCTGCAGTGGGTAGGCTCCGAGCGCCTGCTTCCTGAGCCTACTCCTGCGGTTCC  
 -----+-----+-----+-----+-----+  
                         16030                      16050                      16070  
 CCTCTCTCAGAGCTCTGCTGGGGCTGTGGGAGCTGGGGCAGGCCCTCAGCCTTGCCCCCA  
 -----+-----+-----+-----+-----+  
                         16090                      16110                      16130  
 GGTGCAGAGAGCAGCCCCAGAGGCCATGGAAAGAAGTAGCTTTGAACAGGAGGTTCCAGT  
 -----+-----+-----+-----+-----+  
                         16150                      16170                      16190  
 GGCCTCCCAGTCAAGCGAGGGGGTGGATCCCTGCCCCACCACCAGCACCGCAAGGCATGG  
 -----+-----+-----+-----+-----+  
                         16210                      16230                      16250  
 CCTCTACCTCCCAGTACAGCTCCTCTTGTCCACTCTCCTGCTTCTCCCACCAGCTGGCT

**FIG. 29.28**



[illegible]

**FIG. 29.29**

GGTGGCCAGAGCCTGGCGTGTCAACACGGAGGGGCGCTGCAGAGGGTGGCGGCTGCTTC  
-----+-----+-----+-----+-----+-----+-----+  
16870 16890 16910  
TCATCCCCAGGCGGGAGTCTCAGGGCAGGGGAGAATGTTTTGAAGGAACATCACAGGAAA  
-----+-----+-----+-----+-----+-----+-----+  
16930 16950 16970  
TGACAAGGCCTTGGGGGATGGGATGGGGACAGTCAAAGATGGCTTGAATCATCAAGGGC  
-----+-----+-----+-----+-----+-----+-----+  
16990 17010 17030  
AGCAGGGCACCCAGGGGCAAGGAGAGCAGACATAGCTGCCGAAGGGGCGGACATCCAAGG  
-----+-----+-----+-----+-----+-----+-----+  
17050 17070 17090  
TTCITTTGGAAGCTGAGCGATGCCAGCATCTGGAGAGTGCCAGGCTGCTGGGTGGTGTCTAG  
-----+-----+-----+-----+-----+-----+-----+  
17110 17130 17150  
AGCCTGGAGGAAAATGTTAGGACTAGAGAGAGGAGGTGCCAGCCAGGGCATGAGGCTCAC  
-----+-----+-----+-----+-----+-----+-----+  
17170 17190 17210  
TTGGAGCCTGGATCCCAAGGCTCCCCGTAAGAGGGAGCAGGAAGGGAGCTGAGAGGGTGA  
-----+-----+-----+-----+-----+-----+-----+  
17230 17250 17270  
CTTGGAGCAGATGGGTGCCCAAGAACTCAGTAAACGCAGAACTCCCTGGGTGGACAC  
-----+-----+-----+-----+-----+-----+-----+  
17290 17310 17330  
CATGCTGCGGGGAGGCAATAACCCACTCAGGATCACTGTGCCAACCTCCTGGACTCTTAT  
-----+-----+-----+-----+-----+-----+-----+  
17350 17370 17390  
CACGTTGCTCAGCCCCAAGATGGCCACACAGGGACCACCCCTGGGCGGCGTTCACCC  
-----+-----+-----+-----+-----+-----+-----+

FIG. 29.30

```
17410          17430          17450
CATGGAGTTGGGCCCCACAGCCACTGGACAGCCTGGCCCTGGGTGAGTGAGGCACCAG
-----+-----+-----+-----+-----+-----+-----+-----+

17470          17490          17510
GGGGAGGTGGAGAGGGAAGGGAGAAGGGAAGGGCTCATGCCTCCTGCCTCCTTCCAGATG
-----+-----+-----+-----+-----+-----+-----+-----+

17530          17550          17570
GGCAGCACCCAGTCACCTTGAGTCCCCCTATGCCCCCTCCCCAGCCCCAGGGTCTCCTGCTG
-----+-----+-----+-----+-----+-----+-----+-----+

17590          17610          17630
ACCATATTTCACAACATTTACCTCCACCATTTCTCCAGACCCTGAGAACTCTCATGAGC
-----+-----+-----+-----+-----+-----+-----+-----+

17650          17670          17690
CCAGCAGCCACCCTGAGAAGCCTCTGCCAGCAGTCTCGCCTGACCCCCAAGGTAGGCAGG
-----+-----+-----+-----+-----+-----+-----+-----+

17710          17730          17750
GACCTGGATTCAAAGCCTCCCCCTCTCATCGCCACCCCTCCACCTCTCCACCCCTCAG
-----+-----+-----+-----+-----+-----+-----+-----+

17770          17790          17810
TTTGCTGCCCCCTAATCAGTTTCTGGGCTCAGGTTATTATGAAATGAGTTTATGACCT
-----+-----+-----+-----+-----+-----+-----+-----+

17830          17850          17870
CTTGGTTATCATGAGAGACCAGGATGCTGGAAGCCCTGGGGCTGGGGAGGGAGAAGCTGTG
-----+-----+-----+-----+-----+-----+-----+-----+

17890          17910          17930
GCTTTTCCTGGATCACTGGTCCTCACTGAGTGAGGATGGGCTCTCTGCCACACAGCTTGC
-----+-----+-----+-----+-----+-----+-----+-----+

17950          17970          17990
AGCCTGGGGCCCCAGTCCTTAGGGGACAACATATCCTCCTCATTCTCAGCAGATCAAGTC
-----+-----+-----+-----+-----+-----+-----+-----+
```

FIG. 29.31

```
18010      18030      18050
CAGATGCCAAGATCCTGCCTCTGGTGAGAGGTAGCTCCTAAATGAACAGATTTAAAGAC
-----+-----+-----+-----+-----+-----+-----+

18070      18090      18110
AGGTGGCCACTGACAGCCACTCCAGGAAC TTGAACTGCAGGGGCAGAGCCAGTGAATCAC
-----+-----+-----+-----+-----+-----+-----+

18130      18150      18170
CGGACCTCCAGCACCTGCAGGCAGCTTGGAAAGTTCTTCCCCGAGTGGAGCTTCGACCCA
-----+-----+-----+-----+-----+-----+-----+

18190      18210      18230
CCCACCTCCAGGAACCCAGAGCCACATTAGAAAGTTCTTGAGGGCTGGAGAACACTGCTGGG
-----+-----+-----+-----+-----+-----+-----+

18250      18270      18290
CACACTCTCCAGCTCAATAAACCATCAGTCCCAGAAAGCAAGGTCACACAGCCCCTGACC
-----+-----+-----+-----+-----+-----+-----+

18310      18330      18350
TCCCTCACCAGTGGAGGCTGGGTAGTGCTGGCCATCCCCAAAAGGGCTCTGTCCTGGGAGT
-----+-----+-----+-----+-----+-----+-----+

18370      18390      18410
CTGGTGTGTCTCCTACATGCAATTTCCACGGACCCAGCTCTGTGGAGGGCATGACTGCTG
-----+-----+-----+-----+-----+-----+-----+

18430      18450      18470
GCCAGAAGCTAGTGGTCCTGGGGCCCTATGGTTCGACTGAGTCCACACTCCCCCTGCAGCC
-----+-----+-----+-----+-----+-----+-----+

18490      18510      18530
TGGCTGGCCTCTGCAAAACAAACATAATTTGGGGACCTTCCTTCCTGTCTTCTCCCACCC
-----+-----+-----+-----+-----+-----+-----+

18550      18570      18590
```

FIG. 29.32

TGTCTTCTCCCTAGGTGGTTCCTGAGCCCCACCCCAATCCCAGTGCTACACCTGAGG  
-----+-----+-----+-----+-----+-----+-----+  
18610 18630 18650  
TTCTGGAGCTCAGAATCTGACAGCCTCTCCCCATTCTGTGTGTGTCGGGGGACAGAGG  
-----+-----+-----+-----+-----+-----+-----+  
18670 18690 18710  
GAACCATTTAAGAAAAGATACCAAAGTAGAAGTCAAAAGAAAGACATGTTGGCTATAGGC  
-----+-----+-----+-----+-----+-----+-----+  
18730 18750 18770  
GTGGTGGCTCATGCCATATAATCCCAGCACTTTGGGAAGCQGGGGTAGGAGGATCACCAGA  
-----+-----+-----+-----+-----+-----+-----+  
18790 18810 18830  
GGCCAGCAGGTCCACACCAGCCTGGGCAACACAGCAAGACCCGCATCTACAGAAAAAT  
-----+-----+-----+-----+-----+-----+-----+  
18850 18870 18890  
TTAAATTAGCTGGGCGTGGTGGTGTGTACCTGTAGGCCTAGCTGCTCAGGAGGCTGAAG  
-----+-----+-----+-----+-----+-----+-----+  
18910 18930 18950  
CAGGAGGATCACTTGAGCCTGAGTTCAACACTGCAGTGAGCTATGGTGGCACCCTGCAC  
-----+-----+-----+-----+-----+-----+-----+  
18970 18990 19010  
TCCAGCCTGGGTGACAGAGCAAGACCCCTGTCTCTAAAAATAAATTTTAAAAAGACATATTA  
-----+-----+-----+-----+-----+-----+-----+  
19030 19050 19070  
ACTTGGACCTTGCTTAGTCTTTTCTGTATGTAAATTCAACCCATGGGGTCCCTGAGGAC  
-----+-----+-----+-----+-----+-----+-----+  
19090 19110 19130  
CCACACGGGGTGTTGGTGGGGTGGTGGTGGTGGGGTGGTGGCTGACGGGGTGGT  
-----+-----+-----+-----+-----+-----+-----+

FIG. 29.33

```
19150          19170          19190
GCTGGCAGGCCGAGCCTAGATGGCAGCCAGAGCCCAGGCATGTGTCTGGGCACAGGACG
-----+-----+-----+-----+-----+-----+-----+
19210          19230          19250
GTGTTGCCTAGTTTGAACACCCTCTTTGCTCTGTCACTCCTGCCTCCCTTGGGCGTTTCAC
-----+-----+-----+-----+-----+-----+-----+
19270          19290          19310
ATTCTCCCATTTGCTTCATGCAAGAGCTGCTGAGTGGCCTATATCAGCCAGCTGTTGCCGC
-----+-----+-----+-----+-----+-----+-----+
19330          19350          19370
ATAACAAAACCATCCCAAAACTGAGTGCAGGGAGGCAACTTCACCTCGGGCTCCACTCCA
-----+-----+-----+-----+-----+-----+-----+
19390          19410          19430
CAAGCCCAAGGGGCCAGGTGAGAGTGTCTCTTAAAGCCCCCTCTGCCTCAGTTGTAGTT
-----+-----+-----+-----+-----+-----+-----+
19450          19470          19490
GCAAAATTTTAATTTATGAAGGTGACTGATGACACAGAGGCCAATGCTGTTGAAATAAGT
-----+-----+-----+-----+-----+-----+-----+
19510          19530          19550
TATTACTCACAGTTTCCCACCATGCAGGGCCACAGTGGGGAGGCAC TAGGTTTGGTCCAG
-----+-----+-----+-----+-----+-----+-----+
19570          19590          19610
GGCAGAAATCAGGAGCGAGTGGGAAGGCACAGGCCACAGCCACAGTGCCTGTTTCCACTGG
-----+-----+-----+-----+-----+-----+-----+
19630          19650          19670
GGAGGCAAGGCAGGCCAGGGGAAGAGGGTAGGATTGGCATTTTGAATCATTCTGCTGGGG
-----+-----+-----+-----+-----+-----+-----+
19690          19710          19730
TTTGGGGCGTGGGGTTGGGCTCTAATTGTCTGGGTAGGTGCTGCGCCCTGAGCTGTTTA
-----+-----+-----+-----+-----+-----+-----+
```

FIG. 29.34

19750	19770	19790
GGGCAGGGGAAATACTGGTTTCGTATGTGAGAGTTCCTTGAAGGGGGTGGTTGGTGATAG -----+-----+-----+-----+-----+		
19810	19830	19850
GACTCAAGACTGGTCGGTTTTGCATATGAAAGGCATGAGTTGTTTCTGATCTCCAGGAATC -----+-----+-----+-----+-----+		
19870	19890	19910
AAGCAGTTTCTCTCCAGCCAACAAGCCCCACCCCGAGATGTTAAACCATCATAAAATAG -----+-----+-----+-----+-----+		
19930	19950	19970
AGAATCTAAGGCCAGGCATGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCAAG -----+-----+-----+-----+-----+		
19990	20010	20030
GCGGGAGGATCATTTGAGGTCAGAAGTTCGAGACCAGCCTGGCCAATGTGGTGAAACCCC -----+-----+-----+-----+-----+		
20050	20070	20090
ATCTCTACTAAAAATACAAAAATTAGCCCGGTGTGGTGGCACGTGCCATATAATCCCAGCT -----+-----+-----+-----+-----+		
20110	20130	20150
ACTCGGGAGGCTGCGGCAGGAGAATTGTTTGAACATGGGAGGTGGAGGTTGCAGTGAGCT -----+-----+-----+-----+-----+		
20170	20190	20210
GAGATCGTGCCACTGCACTCCAGCCTGGGCAACAAGAGCAAGACTCCGTCTCAAAAAAAAAA -----+-----+-----+-----+-----+		
20230	20250	20270
AAAAAAAAAAAAAGAGAGACTCTAAAAATACACGTTAATATACCTCCCCCGCTCTTACCCT -----+-----+-----+-----+-----+		
20290	20310	20330

**FIG. 29.35**

TCAGGAGGGGGTGTCTAGACCCCGCGGGACTCCAGCTACAAGGGACCCCTGGGGAGGCCAA  
-----+-----+-----+-----+-----+-----+-----+  
20350 20370 20390  
CTCTGCCCTCTTGGCTAATCCCCAAGACTGCCCAGCACCCCTCCACCCCTTCTCCATTCT  
-----+-----+-----+-----+-----+-----+-----+  
20410 20430 20450  
AGTGGCGAACCCTGGGGAGGCCACGTGGGAAGGAAAGAGGGCTCTAAGAGGGGAGGCCCC  
-----+-----+-----+-----+-----+-----+-----+  
20470 20490 20510  
AGACTGGGGGAGAGGCCTGTCTGGAGCCCAGGATCACCTGGCTGTGCTGCAGAACTGGAG  
-----+-----+-----+-----+-----+-----+-----+  
20530 20550 20570  
AAGAGAAGCTCAGCAGAAAGGAGCTGGCATGGGGCCAAACAGCAGAAAAGCAGGAGGCACG  
-----+-----+-----+-----+-----+-----+-----+  
20590 20610 20630  
CAGAAGTGACTGGGAAGCAGGAGGGTAGGCATGGACCCCTGAGGCTGAGCAGGAGGTACTG  
-----+-----+-----+-----+-----+-----+-----+  
20650 20670 20690  
AGGGGCAGAGTGGACGCTGAGCTGGGGGTAGCGAGCGAGCCAGCTCAGCTGTGACGCCC  
-----+-----+-----+-----+-----+-----+-----+  
20710 20730 20750  
TCTGTTTGGCCACCCAACCTACCAGCTACTTGGGCTGCCCGGGAGGAACCTGGGCTTCCTC  
-----+-----+-----+-----+-----+-----+-----+  
20770 20790 20810  
TGACATTCTGTGGCCTGCGGCCATCTGTGCACACCTTCTTCTCTCTGCCCCCTCCCTTGA  
-----+-----+-----+-----+-----+-----+-----+  
20830 20850 20870  
CTTGTTGGCACCCACAGACAGGTGGGAGAGTGTACCTGCCCTGTGTGGTCAGAGCTTGGTT  
-----+-----+-----+-----+-----+-----+-----+

FIG. 29.36



```
20890          20910          20930
TTGAGTTTCCTTCCCTCACCCCTCTTTCTCTCCACACGCCAAACACAAGAGGATGTGTC
-----+-----+-----+-----+-----+-----+-----+

20950          20970          20990
AGAGGCCCTGTGAACCAGAGCAACTCCATCCTGAATAGGGGCTGAGCAAAATAAGGCTGAG
-----+-----+-----+-----+-----+-----+-----+

21010          21030          21050
ACCTACTGGGGTGC GTTTCAGACAGTTACAGCATTCTGCGTACAGGATGAGATAGGAG
-----+-----+-----+-----+-----+-----+-----+

21070          21090          21110
ATACAGGTCATAAAGACCTTGCTGATAAAATAGTTTGCAGTAGGCCAGGCGCGGTAGCTC
-----+-----+-----+-----+-----+-----+-----+

21130          21150          21170
ACGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGTGGGCGGATCACCTGAGGTCAGAAGT
-----+-----+-----+-----+-----+-----+-----+

21190          21210          21230
TCGAGACCAGCCTGGCCAACAAGGTGAAACCTCATCTCTACTAAAAATACAAAAACTAGC
-----+-----+-----+-----+-----+-----+-----+

21250          21270          21290
CAGGCATGGTGGTGTGTGCCTGTAATCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATCG
-----+-----+-----+-----+-----+-----+-----+

21310          21330          21350
CTTGAACCCAGGAGGTGGAGGTTGCAGTGAGCTGAGATCATGTCACTGCACTCCAGCCTG
-----+-----+-----+-----+-----+-----+-----+

21370          21390          21410
GAGCGAGACTCCGTCTCAAAAACCAAAACCAACCAAAAAAATCAGCTTGCAATATAGAAGC
-----+-----+-----+-----+-----+-----+-----+

21430          21450          21470
TGGCTAAACCCACCCAAACCAAGATGGTGATGAGAGTGACCTCTGGTGGTCCCCACTG
-----+-----+-----+-----+-----+-----+-----+
```

FIG. 29.37

```
      21490                      21510                      21530
CTACACTCCCACCAGCACCATGACAGGTTACAGATGCCATGGCAGTATCAGGAAGTTACC
-----+-----+-----+-----+-----+-----+-----+

      21550                      21570                      21590
ATATATGGTCTAAAAAGGGGAGACATGAACAATCCACCCCTGTTTAGCAGATCATCCAGA
-----+-----+-----+-----+-----+-----+-----+

      21610                      21630                      21650
AACCAACCATAAAATGGGCAACCAGCAGCCCTCAGGGCTGCGCTCTCTATGGAGTAGCCA
-----+-----+-----+-----+-----+-----+-----+

      21670                      21690                      21710
TTCTTTTATTCCTTTTACTTTCTTAATAAATGTGCTTTCACTTTATGGACTCGTCTCAAAT
-----+-----+-----+-----+-----+-----+-----+

      21730                      21750                      21770
TCTTTCTTGACACGAGATCCAAGAACCCTCTCCTGGGGTCTGAATCTGGACCCCTTTCCGG
-----+-----+-----+-----+-----+-----+-----+

      21790                      21810                      21830
TAACAGATGTCGTAGAGTGAAAGCACAACCACTGCAGGGGCATCTTGGTTTACATTTTGCT
-----+-----+-----+-----+-----+-----+-----+

      21850                      21870                      21890
TCAGCGGCCATGGTTAGCACAGCGGAAAGCACATCAGTCTTCTGATTCAATAAAAAAA
-----+-----+-----+-----+-----+-----+-----+

      21910                      21930                      21950
TTAGGAAATGGACCAACCACAAACCACAGACAGATGTACTGAGACAGGATAGGTAGTCAAG
-----+-----+-----+-----+-----+-----+-----+

      21970                      21990                      22010
AAAGTGACCATGTCTAGGCGCGCAGCAGCAACTGTGGTGACCGTACAGTCAACAAGCCT
-----+-----+-----+-----+-----+-----+-----+

      22030                      22050                      22070
```

FIG. 29.38

```
CAGCACTGGCATTGCAATTGAGCTCATTCAAGCAAAGCTATCTTCAGCAGGGACTTCTCC
-----+-----+-----+-----+-----+-----+-----+
22090                22110                22130
CTCTAGGCAGCAAGCGCATTTTTATTTTACCTGTCCTCAAAGTATCCTTTGCTCCTTAT
-----+-----+-----+-----+-----+-----+-----+
22150                22170                22190
AACAGTAAGGAACACACCCCTGTGTGGAGATTTAAGATGCTAATGAGGCCAAGCGCAGTT
-----+-----+-----+-----+-----+-----+-----+
22210                22230                22250
GCTCACGTCTGTAATTCAGCACTTTGGGAGGCAGAGGTGGGCGGGTCACCTGAGGTTAG
-----+-----+-----+-----+-----+-----+-----+
22270                22290                22310
AAGTTCGAGACCAGCCTGGCCAACATGGTGAAACCTTGCTCTACTAAAAATACAAAAAT
-----+-----+-----+-----+-----+-----+-----+
22330                22350                22370
TAGCCGGGCATGGTGGCGGGCGTCTGTAATCCAGCTACCTGGGAGGCTGAGGCAGAAAG
-----+-----+-----+-----+-----+-----+-----+
22390                22410                22430
ATCGCTTGAACCTGGGAGGCGGAGGTTGCAGTGAGCCAAGATCGTGCCACTGCACTCCAG
-----+-----+-----+-----+-----+-----+-----+
22450                22470                22490
CCTGAGGGAGAGAGAGAGACAAACATCGTTTTTGTGTTGTTGTTGTTGTTGTTGTTGTT
-----+-----+-----+-----+-----+-----+-----+
22510                22530                22550
TTTTAAAAAAAAGTCAAGACAAATCATAGTGGGGGCTTTTCTGGTCACTTTTAAATCTT
-----+-----+-----+-----+-----+-----+-----+
22570                22590                22610
AGTGTGAGACTTTATTTGAGACAGGGCCTTACTCTGTGCCCAGGTTGGATGAGATTTT
-----+-----+-----+-----+-----+-----+-----+
```

FIG. 29.39

22630	22650	22670
TAACCTCAATATTTACTTTATAGAATAAAGTTTGGTTAGTCAAAACAATGCTGTGTCTCA -----+-----+-----+-----+-----+		
22690	22710	22730
TTCTGATCAGAATAAAACATCAGACAAGTCAAGAGAAACATTCTGCAAAATAACTGGCCA -----+-----+-----+-----+-----+		
22750	22770	22790
GGATTCTTCAAAGTGTCAGGGGTAAAGATAAGGAAAGATGAAGGAAGTCCCAGATTGAG -----+-----+-----+-----+-----+		
22810	22830	22850
GAGAATAAGGAGACAAGTGTGATGTGGGATCCTAGAATGGATCTTGGAACAGAAAAAGGA -----+-----+-----+-----+-----+		
22870	22890	22910
CATTAGTGAAAAATGAGAAATGC AAAACAGTCTACAGTTTCGTTAACAGGATTGTACCA -----+-----+-----+-----+-----+		
22930	22950	22970
AGGTTAGTTTCTAGCTGTAATGATTGGACTATGATTAAAGTAAGATGGACCATCAGGGGA -----+-----+-----+-----+-----+		
22990	23010	23030
AGCTGGGTGAAGGGTGAAGGAAAATGCTTACATTTTCCAACTTTTCTGCAAGTCTAAAA -----+-----+-----+-----+-----+		
23050	23070	23090
TTAGTCAACAATAAGAAGTTTAAAATAGGCCAGGCATGGTGGCTCACACCTGTCATCCTA -----+-----+-----+-----+-----+		
23110	23130	23150
GCACTTTGAGAGGCCGAGGTGGGAGGATGGTTTTGAGCCCAGGAGTTCAAGACCAGCCTGC -----+-----+-----+-----+-----+		
23170	23190	23210
GCAATAGAGCGAGACCCCAAGTCTATTCAAAAAAATTTTTTAAGTTTAAAATAGAATTA -----+-----+-----+-----+-----+		

**FIG. 29.40**

```
      23230              23250              23270
      .                .                .
TATAAAAAAGGAAAAGAAAAATGCTGTTTCATAGCGTTCCTAGTTTAGCATGGGAGAGAC
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      23290              23310              23330
      .                .                .
CAGGTCCTCCCTGGGTGGTTGCTCTGTGTGTGCTGGGTGTGCGTGCCAGGGCTAGTGTGTT
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      23350              23370              23390
      .                .                .
GGGGTCCGCTCTAGGCACATTCAGGCGCCGAATCCCGTGGCTCCCAGGTTTACCTGACGGT
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      23410              23430              23450
      .                .                .
GCAGCCTGGGGTGGAGACTTAATGAGGGCGGGGAGTTGCTGCAGCAAAGGCTCCTCCCAG
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      23470              23490              23510
      .                .                .
GGGTATCAGCGCAGACAGCTGGGTTTTCACTGTGCTCCTGCTCCAGAGGCACTAGGAAGG
-----+-----+-----+-----+-----+-----+-----+-----+-----+

      23530              23550              23570
      .                .                .
GGGCGCCTATCAGACTAGGACTCTGCCAGCCATCCTTCTGTGTTGAAGGTCCAGC
-----+-----+-----+-----+-----+-----+-----+-----+-----+
```

FIG. 29.41

```

      10                      30                      50
      .                      .                      .
CAGCTATGGGCTGGAGGCCCCGGAGAGCTCGGGGGACCCCGTTGCTGCTGCTGCTACTAC
-----+-----+-----+-----+-----+-----+-----+
      MetGlyTrpArgProArgArgAlaArgGlyThrProLeuLeuLeuLeuLeuLeuL

      70                      90                      110
      .                      .                      .
TGCTGCTGCTCTGGCCAGTGCAGGCGCCGGGGTGCTTCAAGGACATATCCCTGGGCAGC
-----+-----+-----+-----+-----+-----+-----+
      euLeuLeuLeuTrpProValProGlyAlaGlyValLeuGlnGlyHisIleProGlyGlnP

      130                     150                     170
      .                      .                      .
CAGTCACCCCGCACTGGGTCTGGATGGACAACCCCTGGCGCACCGTCAGCCTGGAGGAGC
-----+-----+-----+-----+-----+-----+-----+
      roValThrProHisTrpValLeuAspGlyGlnProTrpArgThrValSerLeuGluGluP

      190                     210                     230
      .                      .                      .
CGGTCTCGAAGCCAGACATGGGGCTGGTGGCCCTGGAGGCTGAAGGCCAGGAGCTCCTGC
-----+-----+-----+-----+-----+-----+-----+
      roValSerLysProAspMetGlyLeuValAlaLeuGluAlaGluGlyGlnGluLeuLeuL

      250                     270                     290
      .                      .                      .
TTGAGCTGGAGAAGAACCACAGGCTGCTGGCCCCAGGATACATAGAAACCCACTACGGCC
-----+-----+-----+-----+-----+-----+-----+
      euGluLeuGluLysAsnHisArgLeuLeuAlaProGlyTyrIleGluThrHisTyrGlyP

      310                     330                     350
      .                      .                      .
CAGATGGGCAGCCAGTGGTCTGGCCCCCAACCACACGGATCATTGCCACTACCAAGGGC
-----+-----+-----+-----+-----+-----+-----+
      roAspGlyGlnProValValLeuAlaProAsnHisThrAspHisCysHisTyrGlnGlyA

      370                     390                     410
      .                      .                      .
GAGTAAGGGGCTTCCCCGACTCCTGGGTAGTCCTCTGCACCTGCTCTGGGATGAGTGGCC
-----+-----+-----+-----+-----+-----+-----+
      rgValArgGlyPheProAspSerTrpValValLeuCysThrCysSerGlyMetSerGlyL

      430                     450                     470
      .                      .                      .
TGATCACCCCTCAGCAGGAATGCCAGCTATTATCTGCGTCCCTGGCCACCCCGGGGCTCCA
-----+-----+-----+-----+-----+-----+-----+
      euIleThrLeuSerArgAsnAlaSerTyrTyrLeuArgProTrpProProArgGlySerL

```

FIG. 30.1

```

      490              510              530
AGGACTTCTCAACCCACGAGATCTTTCGGATGGAGCAGCTGCTCACCTGGAAAGGAACCT
-----+-----+-----+
ysAspPheSerThrHisGluIlePheArgMetGluGlnLeuLeuThrTrpLysGlyThrc

      550              570              590
GTGGCCACAGGGATCCTGGGAACAAAGCGGGCATGACCAGCCTTCCTGGTGGTCCCCAGA
-----+-----+-----+
ysGlyHisArgAspProGlyAsnLysAlaGlyMetThrSerLeuProGlyGlyProGlnS

      610              630              650
GCAGGGGCAGGCGAGAAGCGCGCAGGACCCGGAAGTACCTGGAACCTGTACATTGTGGCAG
-----+-----+-----+
erArgGlyArgArgGluAlaArgArgThrArgLysTyrLeuGluLeuTyrIleValAlaA

      670              690              710
ACCACACCCCTGTCTTGACTCGGCACCGAAACTTGAACCACACCAAACAGCGTCTCCTGG
-----+-----+-----+
spHisThrLeuPheLeuThrArgHisArgAsnLeuAsnHisThrLysGlnArgLeuLeuG

      730              750              770
AAGTCGCCAACTACGTGGACCGAGCTTCTCAGGACTCTGGACATTCAGGTGGCGCTGACCG
-----+-----+-----+
luValAlaAsnTyrValAspGlnLeuLeuArgThrLeuAspIleGlnValAlaLeuThrg

      790              810              830
GCCTGGAGGTGTGGACCGAGCGGGACCGCAGCCGCTCACGCAGGACGCCAACGCCACGC
-----+-----+-----+
lyLeuGluValTrpThrGluArgAspArgSerArgValThrGlnAspAlaAsnAlaThrl

      850              870              890
TCTGGGCCTTCCTGCAGTGGCGCCGGGGGCTGTGGGCGCAGCGGCCCCACGACTCCGCGC
-----+-----+-----+
euTrpAlaPheLeuGlnTrpArgArgGlyLeuTrpAlaGlnArgProHisAspSerAlaG

      910              930              950
AGCTGCTCAGGGCCGCGCCTTCCAGGGCGCCACAGTGGGCCTGGCGCCCGTCGAGGGCA
-----+-----+-----+
lnLeuLeuThrGlyArgAlaPheGlnGlyAlaThrValGlyLeuAlaProValGluGlyM

```

FIG. 30.2

```

      970              990              1010
      .               .               .
TG TGCCGCGCGAGAGCTCGGGAGGCGTGAGCACGGACCACTCGGAGCTCCCCATCGGCG
-----+-----+-----+-----+-----+
etCysArgAlaGluSerSerGlyGlyValSerThrAspHisSerGluLeuProIleGlyA

      1030              1050              1070
      .               .               .
CCGCAGCCACCATTGGCCCATGAGATCGGCCACAGCCTCGGCCTCAGCCACGACCCCGACG
-----+-----+-----+-----+-----+
laAlaAlaThrMetAlaHisGluIleGlyHisSerLeuGlyLeuSerHisAspProAspG

      1090              1110              1130
      .               .               .
GCTGCTGCGTGGAGGCTGCGGCCGAGTCCGGAGGCTGCGTCATGGCTGCGGCCACCGGGC
-----+-----+-----+-----+-----+
lyCysCysValGluAlaAlaAlaGluSerGlyGlyCysValMetAlaAlaAlaThrGlyH

      1150              1170              1190
      .               .               .
ACCCGTTTCCGCGCGTGTTCAGCGCCTGCAGCCGCCGCCAGCTGCGCGCCTTCTTCCGCA
-----+-----+-----+-----+-----+
isProPheProArgValPheSerAlaCysSerArgArgGlnLeuArgAlaPhePheArgL

      1210              1230              1250
      .               .               .
AGGGGGGCGGCGCTTGCCCTCTCCAATGCCCGGACCCCGGACTCCCGGTGCCCGCCGCGC
-----+-----+-----+-----+-----+
ysGlyGlyGlyAlaCysLeuSerAsnAlaProAspProGlyLeuProValProProAlaL

      1270              1290              1310
      .               .               .
TCTGCGGGAACGGCTTCGTGGAAGCGGGCGAGGAGTGTGACTGCGGCCCTGGCCAGGAGT
-----+-----+-----+-----+-----+
euCysGlyAsnGlyPheValGluAlaGlyGluGluCysAspCysGlyProGlyGlnGluC

      1330              1350              1370
      .               .               .
GCCGCGACCTCTGCTGCTTTGCTCACAACCTGCTCGCTGCGCCCCGGGGGCCAGTGCGCCC
-----+-----+-----+-----+-----+
ysArgAspLeuCysCysPheAlaHisAsnCysSerLeuArgProGlyAlaGlnCysAlaH

      1390              1410              1430
      .               .               .
ACGGGGGACTGTGCTGCGTGCGCTGCTGTAAGCCGGCTGGAGCGCTGTGCCGCCAGGCCA
-----+-----+-----+-----+-----+
isGlyAspCysCysValArgCysLeuLeuLysProAlaGlyAlaLeuCysArgGlnAlaM

      1450              1470              1490

```

FIG. 30.3



```

      .      .      .      .      .      .      .      .      .      .
TGGGTGACTGTGACCTCCCTGAGTTTTCACAGGGCACCTCCTCCCAGTGTCCCCAGACG
-----+-----+-----+-----+-----+-----+-----+
etGlyAspCysAspLeuProGluPheCysThrGlyThrSerSerHisCysProProAspV

      1510      1530      1550
      .      .      .      .      .      .      .      .      .      .
TTTACCTACTGGACGGCTCACCTGTGCCAGGGGCAGTGGCTACTGCTGGGATGGCGCAT
-----+-----+-----+-----+-----+-----+-----+
alTyrLeuLeuAspGlySerProCysAlaArgGlySerGlyTyrCysTrpAspGlyAlaC

      1570      1590      1610
      .      .      .      .      .      .      .      .      .      .
GTCCCACGCTGGAGCAGCAGTGCCAGCAGCTCTGGGGGCCCTGGCTCCCACCCAGCTCCCG
-----+-----+-----+-----+-----+-----+-----+
ysProThrLeuGluGlnGlnCysGlnGlnLeuTrpGlyProGlySerHisProAlaProG

      1630      1650      1670
      .      .      .      .      .      .      .      .      .      .
AGGCCTGTTTCCAGGTGGTGAACCTCTGCGGGAGATGCTCATGGAAACTGCGGCCAGGACA
-----+-----+-----+-----+-----+-----+-----+
luAlaCysPheGlnValValAsnSerAlaGlyAspAlaHisGlyAsnCysGlyGlnAspS

      1690      1710      1730
      .      .      .      .      .      .      .      .      .      .
GCGAGGGCCACTTCCTGCCCTGTGCAGGGAGGGATGCCCTGTGTGGGAAGCTGCAGTGCC
-----+-----+-----+-----+-----+-----+-----+
erGluGlyHisPheLeuProCysAlaGlyArgAspAlaLeuCysGlyLysLeuGlnCysG

      1750      1770      1790
      .      .      .      .      .      .      .      .      .      .
AGGGTGGAAAGCCCAGCTGCTGCGACCGCACATGGTGCCAGTGGACTCTACCGTTCACC
-----+-----+-----+-----+-----+-----+-----+
lnGlyGlyLysProSerLeuLeuAlaProHisMetValProValAspSerThrValHisL

      1810      1830      1850
      .      .      .      .      .      .      .      .      .      .
TAGATGGCCAGGAAGTGACTTGTCGGGGAGCCTTGGCACTCCCCAGTGCCCAGCTGGACC
-----+-----+-----+-----+-----+-----+-----+
euAspGlyGlnGluValThrCysArgGlyAlaLeuAlaLeuProSerAlaGlnLeuAspL

      1870      1890      1910
      .      .      .      .      .      .      .      .      .      .
TGCTTGCCCTGGGCTGGTAGAGCCAGGCACCCAGTGTGGACCTAGAAATGGTGTGCCAGA
-----+-----+-----+-----+-----+-----+-----+
euLeuGlyLeuGlyLeuValGluProGlyThrGlnCysGlyProArgMetValCysGlnS

      1930      1950      1970
      .      .      .

```

FIG. 30.4

```

GCAGGCGCTGCAGGAAGAATGCCTTCCAGGAGCTTCAGCGCTGCCTGACTGCCTGCCACA
-----+-----+-----+-----+-----+
erArgArgCysArgLysAsnAlaPheGlnGluLeuGlnArgCysLeuThrAlaCysHisS

      1990                      2010                      2030
GCCACGGGGTTTGCAATAGCAACCATAACTGCCACTGTGCTCCAGGCTGGGCTCCACCTT
-----+-----+-----+-----+-----+
erHisGlyValCysAsnSerAsnHisAsnCysHisCysAlaProGlyTrpAlaProProP

      2050                      2070                      2090
TCTGTGACAAGCCAGGCTTTGGTGGCAGCATGGACAGTGGCCCTGTGCAGGCTGAAAACC
-----+-----+-----+-----+-----+
heCysAspLysProGlyPheGlyGlySerMetAspSerGlyProValGlnAlaGluAsnH

      2110                      2130                      2150
ATGACACCTTCCTGCTGGCCATGCTCCTCAGCGTCCCTGCTGCCTCTGCTCCCAGGGGCCG
-----+-----+-----+-----+-----+
isAspThrPheLeuLeuAlaMetLeuLeuSerValLeuLeuProLeuLeuProGlyAlag

      2170                      2190                      2210
GCCTGGCCTGGTGTGTGCTACCGACTCCCAGGAGCCCATCTGCAGCGATGCAGCTGGGGCT
-----+-----+-----+-----+-----+
lyLeuAlaTrpCysCysTyrArgLeuProGlyAlaHisLeuGlnArgCysSerTrpGlyC

      2230                      2250                      2270
GCAGAAGGGACCCTGCGTGCAGTGGCCCCAAAGATGGCCACACAGGGACCACCCCCTGG
-----+-----+-----+-----+-----+
ysArgArgAspProAlaCysSerGlyProLysAspGlyProHisArgAspHisProLeuG

      2290                      2310                      2330
GCGGCGTTACCCCCATGGAGTTGGGCCCCACAGCCACTGGACAGCCCTGGCCCCCTGGACC
-----+-----+-----+-----+-----+
lyGlyValHisProMetGluLeuGlyProThrAlaThrGlyGlnProTrpProLeuAspP

      2350                      2370                      2390
CTGAGAACTCTCATGAGCCCAGCAGCCACCCTGAGAAGCCTCTGCCAGCAGTCTCGCCTG
-----+-----+-----+-----+-----+
roGluAsnSerHisGluProSerSerHisProGluLysProLeuProAlaValSerProA

      2410                      2430                      2450
ACCCCCAAGATCAAGTCCAGATGCCAAGATCCTGCCTCTGGTGAGAGGTAGCTCCTAAAA

```

FIG. 30.5

```
-----+-----+-----+-----+-----+
spProGlnAspGlnValGlnMetProArgSerCysLeuTrpEnd

      2470              2490              2510
      .               .               .
TGAACAGATTAAAGACAGGTGGCCACTGACAGCCACTCAGGAACCTGAACTGCAGGGG
-----+-----+-----+-----+

      2530              2550              2570
      .               .               .
CAGAGCCAGTGAATCACCGGACCTCCAGCACCTGCAGGCAGCTTGAAGTTTCTTCCCCG
-----+-----+-----+-----+

      2590              2610              2630
      .               .               .
AGTGAGGCTTCGACCCACCCACTCCAGGAACCCAGAGCCACATTAGAAGTTCTTGAGGGC
-----+-----+-----+-----+

      2650              2670              2690
      .               .               .
TGGAGAACACTGCTGGGCACACTCTCCAGCTCAATAAACCATCAGTCCCAGAAGCAAAGG
-----+-----+-----+-----+

      2710              2730              2750
      .               .               .
TCACACAGCCCCCTGACCTCCCTCACCAGTGGAGGCTGGGTAGTGCTGGCCATCCCCAAAG
-----+-----+-----+-----+

      2770              2790              2810
      .               .               .
GGCTCTGTCTCGGGAGTCTGGTGTGTCTCTTACATGCAATTTCACGGACCCAGCTCTGT
-----+-----+-----+-----+

      2830              2850              2870
      .               .               .
GGAGGGCATGACTGCTGGCCAGAAGCTAGTGGTCTCGGGGCCCTATGGTTCGACTGAGTC
-----+-----+-----+-----+

      2890              2910              2930
      .               .               .
CACACTCCCCTGCAGCCTGGCTGGCCTCTGCAAACAAACATAATTTTGGGGACCTTCCTT
-----+-----+-----+-----+

      2950              2970              2990
      .               .               .
CCTGTTTCTTCCCACCCTGTCTTCTCCCTAGGTGGTCTCTGAGCCCCCACCCTCAATCC
-----+-----+-----+-----+
```

FIG. 30.6

```

      3010                      3030                      3050
CAGTGTCTACACCTGAGGTTCTGGAGCTCAGAACTCTGACAGCCTCTCCCCATTCTGTGTG
-----+-----+-----+-----+-----+-----+-----+
      3070                      3090                      3110
TGTCGGGGGGACAGAGGGGAACCATTTAAGAAAAAGATACCAAAGTAGAAGTCAAAAGAAAG
-----+-----+-----+-----+-----+-----+-----+
      3130                      3150                      3170
ACATGTTGGCTATAGGCGTGGTGGCTCATGCCTATAATCCCAGCACTTTGGGAAGCCGGG
-----+-----+-----+-----+-----+-----+-----+
      3190                      3210                      3230
GTAGGAGGATCACCAGAGGCCAGCAGGTCCACACCAGCCTGGGCAACACAGCAAGACACC
-----+-----+-----+-----+-----+-----+-----+
      3250                      3270                      3290
GCATCTACAGAAAAATTTTAAATTAGCTGGGCGTGGTGGTGTGTACCTGTAGGCCTAGC
-----+-----+-----+-----+-----+-----+-----+
      3310                      3330                      3350
TGCTCAGGAGGCTGAAGCAGGAGGATCACTTGAGCCTGAGTTCAACACTGCAGTGAGCTA
-----+-----+-----+-----+-----+-----+-----+
      3370                      3390                      3410
TGGTGGCACCACCTGCACTCCAGCCTGGGTGACAGAGCAAGACCCTGTCTCTAAAAATAAAT
-----+-----+-----+-----+-----+-----+-----+
      3430                      3450                      3470
TTTAAAAAGACATAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
-----+-----+-----+-----+-----+-----+-----+
      3490
AAAAAAAAAAAAAAAAAAAAAAAAAAAA
-----+-----+-----+-----+-----+-----+

```

FIG. 30.7

10 30 50  
CGGGCACGGGTCGGCCGCAATCCAGCCTGGGCGGAGCCGGAGTTGCGAGCCGCTGCCTAG

70 90 110  
AGGCCGAGGAGCTCACAGCTATGGGCTGGAGCCCCGGAGAGCTCGGGGGACCCCGTTGC  
MetGlyTrpArgProArgArgAlaArgGlyThrProLeuL

130 150 170  
TGCTGCTGCTACTACTGCTGCTGCTCTGGCCAGTGCCAGGCGCCGGGGTGCTTCAAGGAC  
euLeuLeuLeuLeuLeuLeuLeuLeuTrpProValProGlyAlaGlyValLeuGlnGlyH

190 210 230  
ATATCCCTGGGCAGCCAGTCACCCCGCACTGGGTCCTGGATGGACAACCCTGGCGCACCG  
isIleProGlyGlnProValThrProHisTrpValLeuAspGlyGlnProTrpArgThrV

250 270 290  
TCAGCCTGGAGGAGCCGGTCTCGAAGCCAGACATGGGGCTGGTGGCCCTGGAGGCTGAAG  
alSerLeuGluGluProValSerLysProAspMetGlyLeuValAlaLeuGluAlaGluG

310 330  
GCCAGGAGCTCCTGCTTGAGCTGGAGAAGAACCACAGGC  
lyGlnGluLeuLeuLeuGluLeuGluLysAsnHisArg

FIG. 31

10 30 50  
CGGGGCACGGGTCGGCCGCAATCCAGCCTGGGCGGAGCCGGAGTTGCGAGCCGCTGCCTAG

70 90 110  
AGGCCGAGGAGCTCACAGCTATGGGCTGGAGGCCCCGGAGAGCTCGGGGGACCCCGTTGC  
MetGlyTrpArgProArgArgAlaArgGlyThrProLeuL

130 150 170  
TGCTGCTGCTACTACTGCTGCTGCTCTGGCCAGTGCCAGGCGCCGGGGGTGCTTCAAGGAC  
euLeuLeuLeuLeuLeuLeuLeuLeuTrpProValProGlyAlaGlyValLeuGlnGlyH

190 210  
ATATCCCTGGGCAGCCAGTCACCCCGCACTGGGTCTCTGGATGGAC  
isIleProGlyGlnProValThrProHisTrpValLeuAspGly

FIG. 32

10 30 50  
 GCCTAGAGGCCGAGGAGCTCACAGCTATGGGCTGGAGGCCCGGAGAGCTCGGGGGACCC  
 MetGlyTrpArgProArgArgAlaArgGlyThrP  
 70 90 110  
 CGTTGCTGCTGCTGCTACTACTGCTGCTGCTCTGGCCAGTGCCAGGCGCCGGGGTGCTTC  
 roLeuLeuLeuLeuLeuLeuLeuLeuLeuLeuTrpProValProGlyAlaGlyValLeuG  
 130 150 170  
 AAGGACATATCCCTGGGCAGCCAGTCACCCCGCACTGGGTCCTGGATGGACAACCCCTGGC  
 lnGlyHisIleProGlyGlnProValThrProHisTrpValLeuAspGlyGlnProTrpA  
 190 210 230  
 GCACCGTCAGCCTGGAGGAGCCGGTCTCGAAGCCAGACATGGGGCTGGTGGCCCTGGAGG  
 rgThrValSerLeuGluGluProValSerLysProAspMetGlyLeuValAlaLeuGluA  
 250 270 290  
 CTGAAGGCCAGGAGCTCCTGCTTGAGCTGGAGAAGAACCACAGGCTGCTGGCCCCAGGAT  
 laGluGlyGlnGluLeuLeuLeuGluLeuGluLysAsnHisArgLeuLeuAlaProGlyT  
 310 330 350  
 ACATAGAAACCCACTACGGCCCAGATGGGCAGCCAGTGGTGCTGGCCCCCAACCACACGG  
 yrIleGluThrHisTyrGlyProAspGlyGlnProValValLeuAlaProAsnHisThrV  
 370 390 410  
 TGAGATGCTTCCATGGGCTCTGGGATGCACCGCCAGAGGATCATTGCCACTACCAAGGGC  
 alArgCysPheHisGlyLeuTrpAspAlaProProGluAspHisCysHisTyrGlnGlyA  
 430 450 470  
 GAGTAAGGGGCTTCCCCGACTCCTGGGTAGTCCTCTGCACCTGCTCTGGGATGAGTGGCC  
 rgValArgGlyPheProAspSerTrpValValLeuCysThrCysSerGlyMetSerGlyL  
 490 510 530  
 TGATCACCCCTCAGCAGGAATGCCAGCTATTATCTGCGTCCCTGGCCACCCCGGGGCTCCA  
 euIleThrLeuSerArgAsnAlaSerTyrTyrLeuArgProTrpProProArgGlySerL  
 550  
 GACTTCTCAACCCACGAGAT  
 AspPheSerThrHisGlu

FIG. 33

10 30 50  
GAGGCCGAGGAGCTCACAGCTATGGGCTGGAGGCCCCGGAGAGCTCGGGGGACCCCGTTG  
MetGlyTrpArgProArgArgAlaArgGlyThrProLeu

70 90 110  
CTGCTGCTGCTACTACTGCTGCTGCTCTGGCCAGTGCCAGGCGCCGGGTGCTTCAAGGA  
LeuLeuLeuLeuLeuLeuLeuLeuLeuTrpProValProGlyAlaGlyValLeuGlnGly

130 150 170  
CATATCCCTGGGCAGCCAGTCACCCCGCACTGGGTCCTGGATGGACAACCCCTGGCGCACC  
HisIleProGlyGlnProValThrProHisTrpValLeuAspGlyGlnProTrpArgThr

190 210 230  
GTCAGCCTGGAGGAGCCGGTCTCGAAGCCAGACATGGGGCTGGTGGCCCTGGAGGCTGAA  
ValSerLeuGluGluProValSerLysProAspMetGlyLeuValAlaLeuGluAlaGlu

250 270 290  
GGCCAGGAGCTCCTGCTTGAGCTGGAGAAGAACCATGGCCTGATCACCCCTCAGCAGGAAT  
GlyGlnGluLeuLeuLeuGluLeuGluLysAsnHisGlyLeuIleThrLeuSerArgAsn

310 330 350  
GCCAGCTATTATCTGCGTCCTGGCCACCCCGGGGCTCCAAGGACTTCTCAACCCACGAG  
AlaSerTyrTyrLeuArgProTrpProProArgGlySerLysAspPheSerThrHisGlu

AT

FIG. 34



10 30 50  
GAGGCCGAGGAGCTCACAGCTATGGGCTGGAGGCCCCGAGAGCTCGGGGGACCCGTTG  
MetGlyTrpArgProArgArgAlaArgGlyThrProLeu

70 90 110  
CTGCTGCTGCTACTACTGCTGCTGCTCTGGCCAGTGCCAGGCGCCGGGGTGCCTTCAAGGA  
LeuLeuLeuLeuLeuLeuLeuLeuLeuTrpProValProGlyAlaGlyValLeuGlnGly

130 150 170  
CATATCCCTGGGCAGCCAGTCACCCGCACTGGGTCTTGGATGGACAACCCTGGCGCACC  
HisIleProGlyGlnProValThrProHisTrpValLeuAspGlyGlnProTrpArgThr

190 210 230  
GTCAGCCTGGAGGAGCCGGTCTCGAAGCCAGACATGGGGCTGGTGGCCCTGGAGGCTGAA  
ValSerLeuGluGluProValSerLysProAspMetGlyLeuValAlaLeuGluAlaGlu

250 270 290  
GGCCAGGAGCTCCTGCTTGAGCTGGAGAAGAACCACAGGCTGCTGGCCCCAGGATACATA  
GlyGlnGluLeuLeuLeuGluLeuGluLysAsnHisArgLeuLeuAlaProGlyTyrIle

310 330 350  
GAAACCCACTACGGCCCAGATGGGCAGCCAGTGGTGCTGGCCCCCAACCACACGGATCAT  
GluThrHisTyrGlyProAspGlyGlnProValValLeuAlaProAsnHisThrAspHis

370 390 410  
TGCCACTACCAAGGGCGAGTAAGGGGCTTCCCCGACTCCTGGGTAGTCTCTGCACCTGC  
CysHisTyrGlnGlyArgValArgGlyPheProAspSerTrpValValLeuCysThrCys

430 450 470  
TCTGGGATGAGTGGCCTGATCACCCCTCAGCAGGAATGCCAGCTATTATCTGCGTCCCTGG  
SerGlyMetSerGlyLeuIleThrLeuSerArgAsnAlaSerTyrTyrLeuArgProTrp

490 510  
CCACCCGGGGCTCCAAGGACTTCTCAACCCACGAGAT  
ProProArgGlySerLysAspPheSerThrHisGlu

FIG. 35

10 30 50  
CTGGCCCCAGGATACATAGAAACCCACTACGGCCCAGATGGGCAGCCAGTGGTGCTGGCC  
LeuAlaProGlyTyrIleGluThrHisTyrGlyProAspGlyGlnProValValLeuAla

70 90 110  
CCCAACCACACGGATCATTGCCACTACCAAGGGCGAGTAAGGGGCTTCCCGACTCCTGG  
ProAsnHisThrAspHisCysHisTyrGlnGlyArgValArgGlyPheProAspSerTrp

130 150 170  
GTAGTCCTCTGCACCTGCTCTGGGATGAGTGGCCTGATCACCTCAGCAGGAATGCCAGC  
ValValLeuCysThrCysSerGlyMetSerGlyLeuIleThrLeuSerArgAsnAlaSer

190 210 230  
TATTATCTGCGTCCCTGGCCACCCCGGGGCTCCAAGGACTTCTCAACCCACGAGATCTTT  
TyrTyrLeuArgProTrpProProArgGlySerLysAspPheSerThrHisGluIlePhe

250 270 290  
CGGATGGAGCAGCTGCTCACCTGGAAAGGAACCTGTGGCCACAGGGATCCTGGGAACAAA  
ArgMetGluGlnLeuLeuThrTrpLysGlyThrCysGlyHisArgAspProGlyAsnLys

310 330 350  
GCGGGCATGACCAGCCTTCTGGTGGTCCCCAGAGCAGGGGCAGGCGAAAAGCGCGCAGG  
AlaGlyMetThrSerLeuProGlyGlyProGlnSerArgGlyArgArgLysAlaArgArg  
Glu

370 390 410  
ACCCGGAAGTACCTGGAACCTGTACATTGTGGCAGACCACACCTGTTCCTGACTCGGCAC  
ThrArgLysTyrLeuGluLeuTyrIleValAlaAspHisThrLeuPheLeuThrArgHis

430 450 470  
CGAAACTTGAACCACACCAAAACAGCGTCTCCTGGAAGTCGCCAACTACGTGGACCAGCTT  
ArgAsnLeuAsnHisThrLysGlnArgLeuLeuGluValAlaAsnTyrValAspGlnLeu

490  
CTCAGGACTCTGGACATTTCAGGTGGC  
LeuArgThrLeuAspIleGlnVal

FIG. 36

10 30 50  
CAGTGGCTACTGCTGGGATGGCGCATGTCCACGCTGGAGCAGCAGTGCCAGCAGCTCTG  
SerGlyTyrCysTrpAspGlyAlaCysProThrLeuGluGlnGlnCysGlnGlnLeuTr

70 90 110  
GGGGCCTGGCTCCCACCCAGCTCCCGAGGCCTGTTTCCAGGTGGTGAACCTCTGCGGGAGA  
pGlyProGlySerHisProAlaProGluAlaCysPheGlnValValAsnSerAlaGlyAs

130 150 170  
TGCTCATGGAAACTGCGGCCAGGACAGCGAGGGCCACTTCCTGCCCTGTGCAGGGAGGGA  
pAlaHisGlyAsnCysGlyGlnAspSerGluGlyHisPheLeuProCysAlaGlyArgAs

190 210 230  
TGCCCTGTGTGGGAAGCTGCAGTGCCAGGGTGGAAGCCCAGCCTGCTCGCACCGCACAT  
pAlaLeuCysGlyLysLeuGlnCysGlnGlyGlyLysProSerLeuLeuAlaProHisMe

250 270 290  
GGTGCCAGTGGACTCTACCGTTCACCTAGATGGCCAGGAAGTGACTTGTCTGGGGAGCCTT  
tValProValAspSerThrValHisLeuAspGlyGlnGluValThrCysArgGlyAlaLe

310 330 350  
GGCACTCCCCAGTGCCAGCTGGACCTGCTTGGCCTGGGCCTGGTAGAGCCAGGCACCCA  
uAlaLeuProSerAlaGlnLeuAspLeuLeuGlyLeuGlyLeuValGluProGlyThrGl

370 390 410  
GTGTGGACCTAGAATGGTTTGC AATAGCAACCATAACTGCCACTGTGCTCCAGGCTGGGC  
nCysGlyProArgMetValCysAsnSerAsnHisAsnCysHisCysAlaProGlyTrpAl

430 450 470  
TCCACCCTTCTGTGACAAGCCAGGCTTGGTGGCAGCATGGACAGTGGCCCTGTGCAGGC  
aProProPheCysAspLysProGlyPheGlyGlySerMetAspSerGlyProValGlnAl

490  
TGAAAACCATGACACCTTCCTGC  
aGluAsnHisAspThrPheLeu

FIG. 37



10 30 50  
CAGTGGCTACTGCTGGGATGGCGCATGTCCCACGCTGGAGCAGCAGTGCCAGCAGCTCTG  
SerGlyTyrCysTrpAspGlyAlaCysProThrLeuGluGlnGlnCysGlnGlnLeuTr

70 90 110  
GGGGCCTGATGGCCAGGAAGTGACTTGTCGGGGAGCCTTGCCACTCCCCAGTGCCCAGCT  
pGlyProAspGlyGlnGluValThrCysArgGlyAlaLeuAlaLeuProSerAlaGlnLe

130 150 170  
GGACCTGCTTGGCCTGGGCCTGGTAGAGCCAGGCACCCAGTGTGGACCTAGAATGGTGTG  
uAspLeuLeuGlyLeuGlyLeuValGluProGlyThrGlnCysGlyProArgMetValCy

190 210 230  
CCAGAGCAGGCGCTGCAGGAAGAATGCCTTCCAGGAGCTTCAGCGCTGCCTGACTGCCTG  
sGlnSerArgArgCysArgLysAsnAlaPheGlnGluLeuGlnArgCysLeuThrAlaCy

250 270 290  
CCACAGCCACGGGGTTTGCAATAGCAACCATAACTGCCACTGTGCTCCAGGCTGGGCTCC  
sHisSerHisGlyValCysAsnSerAsnHisAsnCysHisCysAlaProGlyTrpAlaPr

310 330 350  
ACCCTTCTGTGACAAGCCAGGCTTTGGTGGCAGCATGGACAGTGGCCCTGTGCAGGCTGA  
oProPheCysAspLysProGlyPheGlyGlySerMetAspSerGlyProValGlnAlaGl

370  
AAACCATGACACCTTCCTGC  
uAsnHisAspThrPheLeu

FIG. 39

10 30 50  
GGCCTGGTGTGTGCTACCGACTCCCAGGAGCCCATCTGCAGCGATGCAGCTGGGGCTGCAG  
AlaTrpCysCysTyrArgLeuProGlyAlaHisLeuGlnArgCysSerTrpGlyCysAr

70 90 110  
AAGGGACCCGTGCGTGCA GTGGCCCCAAAGATGGCCCACACAGGGACCACCCCTGGGCGG  
gArgAspProAlaCysSerGlyProLysAspGlyProHisArgAspHisProLeuGlyGl

130 150 170  
CGTTCACCCCATGGAGTTGGGCCCCACAGCCACTGGACAGCCCTGGCCCCCTGGACCCTGA  
yValHisProMetGluLeuGlyProThrAlaThrGlyGlnProTrpProLeuAspProGl

190 210 230  
GAACTCTCATGAGCCCAGCAGCCACCCTGAGAAGCCTCTGCCAGCAGTCTCGCCTGACCC  
uAsnSerHisGluProSerSerHisProGluLysProLeuProAlaValSerProAspPr

250 270 290  
CCAAGCAGATCAAGTCCAGATGCCAAGATCCTGCCTCTGGTGAGAGGTAGCTCCTAAAAAT  
oGlnAlaAspGlnValGlnMetProArgSerCysLeuTrpEnd

310  
GAACAGATTTTAAAGACAGGTGGCC

FIG. 40

```

      10              30              50
CAGTGGCTACTGCTGGGATGGCGCATGTCCCACGCTGGAGCAGCAGTGCCAGCAGCTCTG
SerGlyTyrCysTrpAspGlyAlaCysProThrLeuGluGlnGlnCysGlnGlnLeuTr

      70              90              110
GGGGCCTGATGGCCAGGAAGTGACTTGTCGGGGAGCCTTGCGCACTCCCCAGTGCCCAGCT
pGlyProAspGlyGlnGluValThrCysArgGlyAlaLeuAlaLeuProSerAlaGlnLe

     130             150             170
GGACCTGCTTGGCCTGGGCTGGTAGAGCCAGGCACCCAGTGTGGACCTAGAATGGTGTG
uAspLeuLeuGlyLeuGlyLeuValGluProGlyThrGlnCysGlyProArgMetValCy

     190             210             230
CCAGAGCAGGCGCTGCAGGAAGAATGCCTTCCAGGAGCTTCAGCGCTGCCTGACTGCCTG
sGlnSerArgArgCysArgLysAsnAlaPheGlnGluLeuGlnArgCysLeuThrAlaCy

     250             270             290
CCACAGCCACGGGGTTTGCAATAGCAACCATAACTGCCACTGTGCTCCAGGCTGGGCTCC
sHisSerHisGlyValCysAsnSerAsnHisAsnCysHisCysAlaProGlyTrpAlaPr

     310             330             350
ACCCCTTCTGTGACAAGCCAGGCTTGGTGGCAGCATGGACAGTGCCCTGTGCAGGCTGA
oProPheCysAspLysProGlyPheGlyGlySerMetAspSerGlyProValGlnAlaGl

     370             390             410
AAACCATGACACCTTCTCTGCTGGCCATGCTCCTCAGCGTCCTGCTGCCTCTGCTCCCAGG
uAsnHisAspThrPheLeuLeuAlaMetLeuLeuSerValLeuLeuProLeuLeuProGl

     430             450             470
GGCCGGCCTGGCCTGGTGTGCTACCGACTCCCAGGAGCCCATCTGCAGCGATGCAGCTG
yAlaGlyLeuAlaTrpCysCysTyrArgLeuProGlyAlaHisLeuGlnArgCysSerTr

     490             510             530
GGGTGCAGAAGGGACCTGCGTGCAGTGGCCCAAAGATGGCCACACAGGGACCACCC
pGlyCysArgArgAspProAlaCysSerGlyProLysAspGlyProHisArgAspHisPr

     550             570             590
CCTGGCGGGCGTTACCCCCATGGAGTTGGGCCCCACAGCCACTGGACAGCCCTGGCCCCCT
oLeuGlyGlyValHisProMetGluLeuGlyProThrAlaThrGlyGlnProTrpProLe

     610             630             650
GGACCTTGAGAACTCTCATGAGCCCAGCAGCCACCCTGAGAAGCCTTGCCAGCAGTCTC
uAspProGluAsnSerHisGluProSerSerHisProGluLysProLeuProAlaValSe

     670             690             710
GCCTGACCCCCAAGCAGATCAAGTCCAGATGCCAAGATCCTGCCTCTGGTGAGAGGTAGC
rProAspProGlnAlaAspGlnValGlnMetProArgSerCysLeuTrpEnd

     730             750
TCCTAAATGAACAGATTTAAAGACAGGTGGCC

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FIG. 41

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      10                               30                               50
      .                               .                               .
CAGTGGCTACTGCTGGGATGGCGCATGTCCCACGCTGGAGCAGCAGTGCCAGCAGCTCTG
SerGlyTyrCysTrpAspGlyAlaCysProThrLeuGluGlnGlnCysGlnGlnLeuTr

      70                               90                               110
      .                               .                               .
GGGGCCTGGCTCCCACCCAGCTCCCGAGGCCTGTTCCAGGTGGTGAACCTCTGCGGGAGA
pGlyProGlySerHisProAlaProGluAlaCysPheGlnValValAsnSerAlaGlyAs

      130                              150                              170
      .                               .                               .
TGCTCATGGAAACTGCGGCCAGGACAGCGAGGGCCACTTCCTGCCCTGTGCGAGGGAGGGA
pAlaHisGlyAsnCysGlyGlnAspSerGluGlyHisPheLeuProCysAlaGlyArgAs

      190                              210                              230
      .                               .                               .
TGCCCTGTGTGGGAAGCTGCAGTGCCAGGGTGGAAAGCCCAGCCTGCTCGCACCCGCACAT
pAlaLeuCysGlyLysLeuGlnCysGlnGlyGlyLysProSerLeuLeuAlaProHisMe

      250                              270                              290
      .                               .                               .
GGTGCCAGTGGACTCTACCGTTCACCTAGATGGCCAGGAAGTGACTTGTCGGGGAGCCTT
tValProValAspSerThrValHisLeuAspGlyGlnGluValThrCysArgGlyAlaLe

      310                              330                              350
      .                               .                               .
GGCACTCCCCAGTGCCCACTGGACCTGCTTGGCCTGGGGCCTGGTAGAGCCAGGCACCCA
uAlaLeuProSerAlaGlnLeuAspLeuLeuGlyLeuGlyLeuValGluProGlyThrGl

      370                              390                              410
      .                               .                               .
GTGTGGACCTAGAATGGTGTGCCAGAGCAGGCGCTGCAGGAAGAATGCCTTCCAGGAGCT
nCysGlyProArgMetValCysGlnSerArgArgCysArgLysAsnAlaPheGlnGluLe

      430                              450                              470
      .                               .                               .
TCAGCGCTGCCTGACTGCCTGCCACAGCCACGGGGTTTGCAATAGCAACCATAACTGCCA
uGlnArgCysLeuThrAlaCysHisSerHisGlyValCysAsnSerAsnHisAsnCysHi

      490                              510                              530
      .                               .                               .
CTGTGCTCCAGGCTGGGCTCCACCCTTCTGTGACAAGCCAGGCTTTGGTGGCAGCATGGA
sCysAlaProGlyTrpAlaProProPheCysAspLysProGlyPheGlyGlySerMetAs

      550                              570                              590
      .                               .                               .
CAGTGGCCCTGTGCAGGCTGAAAACCATGACACCTTCCTGCTGGCCATGCTCCTCAGCGT
pSerGlyProValGlnAlaGluAsnHisAspThrPheLeuLeuAlaMetLeuLeuSerVa

      610                              630                              650
      .                               .                               .
CCTGCTGCCTCTGCTCCCAGGGCCGGCCTGGCCTGGTGTGTGCTACCGACTCCCAGGAGC
lLeuLeuProLeuLeuProGlyAlaGlyLeuAlaTrpCysCysTyrArgLeuProGlyAl

```

FIG. 42.1



CCATCTGCAGCGATGCAGCTGGGGCTGCAGAAGGGACCCCTGCGTGCAGTGGCCCCAAAGA  
aHisLeuGlnArgCysSerTrpGlyCysArgArgAspProAlaCysSerGlyProLysAs  
730 750 770  
TGGCCACACAGGGACCACCCCTGGGCGGCGTTACCCCATGGAGTTGGGCCCCACAGC  
pGlyProHisArgAspHisProLeuGlyGlyValHisProMetGluLeuGlyProThrAl  
790 810 830  
CACTGGACAGCCCTGGCCCCCTGGACCCTGAGAACTCTCATGAGCCCAGCAGCCACCCCTGA  
aThrGlyGlnProTrpProLeuAspProGluAsnSerHisGluProSerSerHisProGl  
850 870 890  
GAAGCCTCTGCCAGCAGTCTCGCCTGACCCCCAAGATCAAGTCCAGATGCCAAGATCCTG  
uLysProLeuProAlaValSerProAspProGlnAspGlnValGlnMetProArgSerCy  
910 930 950  
CCTCTGGTGAGAGGTAGCTCCTAAATGAACAGATTTAAAGACAGGTGGCCACTGACAGC  
sLeuTrpEnd  
970 990 1010  
CACTCCAGGAACCTGAACTGCAGGGGCAGAGCCAGTGAATCACCGGACTCCAGCACCTG  
1030 1050 1070  
CAGGCAGCTTGGAAGTTTCTTCCCCGAGTGGAGCTTCGACCCACCCACTCCAGGAACCCA  
1090 1110 1130  
GAGCCACATTAGAAGTTCCTGAGGGCTGGAGAACACTGCTGGGCACACTCTCCAGCTCAA  
1150  
TAAACCATCAGTCC

FIG. 42.2

10 30 50  
 CAGTGGCTACTGCTGGGATGGCGCATGTCCACGCTGGAGCAGCAGTGCCAGCAGCTCTG  
 SerGlyTyrCysTrpAspGlyAlaCysProThrLeuGluGlnGlnCysGlnGlnLeuTr

70 90 110  
 GGGGCCTGATGGCCAGGAAGTGACTTGTCGGGGAGCCTTGCCACTCCCCAGTGCCCAGCT  
 pGlyProAspGlyGlnGluValThrCysArgGlyAlaLeuAlaLeuProSerAlaGlnLe

130 150 170  
 GGACCTGCTTGGCCTGGGCTGGTAGAGCCAGGCACCCAGTGTGGACCTAGAATGGTGTG  
 uAspLeuLeuGlyLeuGlyLeuValGluProGlyThrGlnCysGlyProArgMetValCy

190 210 230  
 CCAGAGCAGGCGCTGCAGGAAGAATGCCTTCCAGGAGCTTCAGCGCTGCCCTGACTGCCTG  
 sGlnSerArgArgCysArgLysAsnAlaPheGlnGluLeuGlnArgCysLeuThrAlaCy

250 270 290  
 CCACAGCCACGGGGTTTGCAATAGCAACCATAACTGCCACTGTGCTCCAGGCTGGGCTCC  
 sHisSerHisGlyValCysAsnSerAsnHisAsnCysHisCysAlaProGlyTrpAlaPr

310 330 350  
 ACCCTTCTGTGACAAGCCAGGCTTTGGTGGCAGCATGGACAGTGGCCCTGTGCAGGCTGA  
 oProPheCysAspLysProGlyPheGlyGlySerMetAspSerGlyProValGlnAlaGl

370 390 410  
 AAACCATGACACCTTCCTGCTGGCCATGCTCCTCAGCGTCCTGCTGCCTCTGCTCCCAGG  
 uAsnHisAspThrPheLeuLeuAlaMetLeuLeuSerValLeuLeuProLeuLeuProGl

430 450 470  
 GGCCGGCCTGGCCTGGTGTGCTACCGACTCCCAGGAGCCCATCTGCAGCGATGCAGCTG  
 yAlaGlyLeuAlaTrpCysCysTyrArgLeuProGlyAlaHisLeuGlnArgCysSerTr

490 510 530  
 GGGCTGCAGAAGGGACCCTGCGTGCAGTGGCCCCAAAGATGGCCACACAGGGACCACCC  
 pGlyCysArgArgAspProAlaCysSerGlyProLysAspGlyProHisArgAspHisPr

FIG. 43.1

CCTGGGCGGCGTTCACCCCATGGAGTTGGGCCCCACAGCCACTGGACAGCCCTGGCCCCCT  
oLeuGlyGlyValHisProMetGluLeuGlyProThrAlaThrGlyGlnProTrpProLe

610 630 650

GGACCCTGAGAACTCTCATGAGCCCAGCAGCCACCCTGAGAAGCCTCTGCCAGCAGTCTC  
uAspProGluAsnSerHisGluProSerSerHisProGluLysProLeuProAlaValSe

670 690 710

GCCTGACCCCCAAGATCAAGTCCAGATGCCAAGATCCTGCCTCTGGTGAGAGGTAGCTCC  
rProAspProGlnAspGlnValGlnMetProArgSerCysLeuTrpEnd

730 750 770

TAAAATGAACAGATTTAAAGACAGGTGGCCACTGACAGCCACTCCAGGAACCTGAACTGC

790 810 830

AGGGGCAGAGCCAGTGAATCACCGGACCTCCAGCACCTGCAGGCAGCTTGGAAGTTTCTT

850 870 890

CCCCGAGTGGAGCTTCGACCCACCCACTCCAGGAACCCAGAGCCACATTAGAAGTTCCTG

910 930 950

AGGGCTGGAGAACTGCTGGGCACACTCTCCAGCTCAATAAACCATCAGTCC

FIG. 43.2

## SEQUENCE LISTING

<110> SCHERING CORPORATION  
GENOME THERAPEUTICS CORPORATION

<120> NOVEL HUMAN GENE RELATING TO RESPIRATORY DISEASES,  
OBESITY, AND INFLAMMATORY BOWEL DISEASE

<130> 2976-4039PC2

<140>

<141>

<150> 09/834,597

<151> 2001-04-13

<160> 420

<170> PatentIn Ver. 2.1

<210> 1

<211> 3626

<212> DNA

<213> Homo sapiens

<400> 1

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gagtaaggggg	cttccccgcac	tccctgggtag	tcctctgcac	ctgctctggg	atgagtggcc	420
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c a a t g t g g c t	t t g c c t t t g t	a a c g t g t a t g	g c a g a g g a g t	c t g t a g c a c a	t g c a t g c t g c	29580
a c a g a a g a t t	g g a g t g g g g a	t g g a c t g t a t	c a c t c a t g a a	a g a c a t t t g c	a a a a g c a c t g	29640
t t g a a g c a a	g t t g g c a t g t	a a c a g a t t t g	g t c a t t a t a a	a c g t a t t c a c	t t c t t c a g t g	29700
a g c a t t t g c c	a t g t g a a a g c	c t g t a g g g c c	a c a c a a a g a a	c t t c a a t t c t	a g a g t a a g g t	29760
g g a t g t a a g t	g a a a c a a a c c	c a c a t a t a a c	a a c t g a a a g c	c a g a g t g t g g	a a a g t g a c a t	29820
g a g a t g a t c c	c a g a a a t g c t	a t c a a a g t t t	a a a g g a g g a c	a a a t g g g g a g	a c t a t g t t g a	29880
a g a a c a t c a g	c c t t c t a g t c	a g a c a g a g g t	g g a t t g a t t c	c t g g c t c c t a	t a c a a a t c a t	29940
a c a g c t t t t c	c a a g t c t c c a	g t t c t c t g t g	c a t g t g a c c t	g a a g g g t a g t	t g t a a g g g g c	30000
t g t g c a g c t g	c t g c a g t g t c	t t g t t a g c c t	g c t c c t t t c c	t c t g t t c c c a	g g g g g c c a g t	30060
g t a c t c c c t c	t t g t c g g a g a	c c c a t g g c c c	c a t t t t a a c t	t t t t a t a c t c	a t g t c c c c t g	30120
g g g c c t t t c c	t c a a t a c c t t	c t g c t t c t t a	c c t t c t t c a t	t a g g t g a a t	g t g g a g g t t a	30180
g g g a t a g g t g	g g c t t t c a a g	g a c t g g t t c a	c c t t t a a c c a	t g g a a g c a t g	g t c a c t g g a c	30240
g g a g g c t g t t	g c t g t t t g c c	a a t g t t c a g a	a g c a t a a t c a	a c c t c a g a a g	c a a g t c a c c a	30300
c a a a c a t a t g	a a a a a a g t t c	a a c a t c a c t g	a t c a t t a g a g	a a a t g c a a a g	c a g a a c c a c a	30360
g t g a g a t a c c	a t c t c a c a c c	a g t c a g a a t g	t c t g t t a t t a	a a a a g t c a a a	a a g a a c a g a	30420
t g c t g g c a a g	g c t g t g g a g a	a a c a g g a a c g	c t t t t a c a c t	g t t g g t g g g a	g t g t a a a t t a	30480
g t t c a a c c a t	t g t g g a a g a c	a g t c t g g c a a	t t c c t c a a a g	a c c t a g a g g c	a g a a a t a c c a	30540
t t t g a c c c a g	c c a t c c c a t t	a c t g g g t g t a	t a t c a a a a a g	a a t a t a a a t c	a t t c t g t a a c	30600
a a a g a t a c a t	g c a c a t g t a t	g t t c a t t g c a	g c a c t a t t c a	c a g t a g c a a a	g a c a t a g a a t	30660
c a a c c t a a a t	g c c c a t c a g t	g a t a g a c t g g	a t a a a g a a a a	t g t g g t a c a t	a t a c a c c a t g	30720
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c t g g a g g c c a	t t a t c c t c a g	c a a a c t a a t g	c a g g a a c g g a	a a a c c a g g t a	c c a c a t g t t c	30840
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a a a a a a g c a a	g t t a t c a c t c	a t c a a t t a g g	a t g c c t t g g g	a c t g t g a c t a	a a g a a c a g t t	31140
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a t t g a t a c a t	a a t t g t a c g t	a t t t a t g a g g	t a c a t g a g a t	a t t t t g a t a c	a t g c a t a c a a	32340
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```

&lt;210&gt; 7

&lt;211&gt; 65

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 7

```

agtctccgtg ctcttagccc tcttcaccaa caggaaacca atatgattag tttctttcat 60
aggct 65

```

&lt;210&gt; 8

&lt;211&gt; 656

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 8

```

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&lt;210&gt; 9

&lt;211&gt; 177

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 9

```

ggggcacggg tcggccgcaa tccagcctgg gcggagccgg agttgcgagc cgctgcctag 60

```



aggcccgagga gctcacagct atgggctgga ggccccggag agctcggggg accccgttgc 120  
 tgctgctgct actactgctg ctgctctggc cagtgccagg cgccgggggtg cttcaag 177

<210> 10  
 <211> 80  
 <212> DNA  
 <213> Homo sapiens

<400> 10  
 gacatatccc tgggcagcca gtcaccccgc actgggtcct ggatggacaa ccttggcgca 60  
 ccgtcagcct ggaggagccg 80

<210> 11  
 <211> 77  
 <212> DNA  
 <213> Homo sapiens

<400> 11  
 gtctcgaagc cagacatggg gctggtggcc ctggaggctg aaggccagga gctcctgctt 60  
 gagctggaga agaacca 77

<210> 12  
 <211> 79  
 <212> DNA  
 <213> Homo sapiens

<400> 12  
 caggctgctg gccccaggat acatagaaac ccactacggc ccagatgggc agccagtggg 60  
 gctggccccc aaccacacg 79

<210> 13  
 <211> 119  
 <212> DNA  
 <213> Homo sapiens

<400> 13  
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 gctggccccc aaccacacg tgagatgctt ccatgggctc tgggatgcac cgccagagg 119

<210> 14  
 <211> 77  
 <212> DNA  
 <213> Homo sapiens

<400> 14  
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 acctgctctg ggatgag 77

<210> 15

<211> 190  
 <212> DNA  
 <213> Homo sapiens

<400> 15  
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 aacctgtggc cacagggatc ctgggaacaa agcgggcatg accagccttc ctggtggtcc 180  
 ccagagcagg 190

<210> 16  
 <211> 66  
 <212> DNA  
 <213> Homo sapiens

<400> 16  
 ggcaggcgag aagcgcgag gaccgggaag tacctggaac tgtacattgt ggcagaccac 60  
 accctg 66

<210> 17  
 <211> 72  
 <212> DNA  
 <213> Homo sapiens

<400> 17  
 ttcttgactc ggcaccgaaa ctggaaccac accaaacagc gtctcctgga agtcgccaac 60  
 tacgtggacc ag 72

<210> 18  
 <211> 167  
 <212> DNA  
 <213> Homo sapiens

<400> 18  
 cttctcagga ctctggacat tcagggtggc ctgaccggcc tggaggtgtg gaccgagcgg 60  
 gaccgcagcc gcgtcacgca ggacgccaac gccacgctct gggccttcct gcagtggcgc 120  
 cggggggctgt gggcgccagc gccccacgac tcgcgcagc tgcac 167

<210> 19  
 <211> 85  
 <212> DNA  
 <213> Homo sapiens

<400> 19  
 gggccgcgcc ttccaggcgc ccacagtggg cctggcgccc gtcgagggca tgtgccgcgc 60  
 cgagagctcg ggaggcgtga gcacg 85

<210> 20  
 <211> 143  
 <212> DNA

<213> Homo sapiens

<400> 20

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gaccactcgg agctcccat cgcgccgca gccaccatgg cccatgagat cggccacagc 60
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tgcgtcatgg ctgcggccac cgg                                     143
```

<210> 21

<211> 178

<212> DNA

<213> Homo sapiens

<400> 21

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gcacccggtt ccgcgcgtgt tcagcgctg cagccgccgc cagctgcgcg ccttcttccg 60
caaggggggc ggcgcttgcc tctccaatgc cccggacccc ggactcccgg tgccgccggc 120
gctctgcggg aacggcttcg tggaaagcgg cgaggagtgt gactgcggcc ctggccag 178
```

<210> 22

<211> 90

<212> DNA

<213> Homo sapiens

<400> 22

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gagtgcgcgc acctctgctg ctttgctcac aactgctcgc tgcgcccggg ggcccagtcg 60
gccacgggg actgctgcgt gcgctgcctg                                     90
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<210> 23

<211> 196

<212> DNA

<213> Homo sapiens

<400> 23

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ctgaagccgg ctggagcgt gtgcgccag gccatgggtg actgtgacct cctgagttt 60
tgcacgggca cctcctccca ctgtcccca gacgtttacc tactggacgg ctcaccctgt 120
gccaggggca gtggctactg ctgggatggc gcatgtccca cgtggagca gcagtgccag 180
cagctctggg ggcctg                                     196
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<210> 24

<211> 107

<212> DNA

<213> Homo sapiens

<400> 24

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gtccccacc agctcccgag gcctgtttcc aggtggtgaa ctctgcggga gatgctcatg 60
gaaactgcgg ccaggacagc gagggccact tctgccctg tgcaggg                                     107
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<210> 25

<211> 199

<212> DNA

<213> Homo sapiens

```

<400> 25
ggatgccctg tgtgggaagc tgcagtgcc a ggttgaaag ccagcctgc tcgcaccgca 60
catggtgcc a tggactcta ccgttcacct agatggccag gaagtgactt gtcggggagc 120
cttggcactc ccagtgccc agctggacct gcttggcctg ggctggtag agccaggcac 180
ccagtggtga cctagaatg                                     199

```

```

<210> 26
<211> 109
<212> DNA
<213> Homo sapiens

```

```

<400> 26
gtttgcaata gcaaccataa ctgccactgt gctccaggct gggctccacc cttctgtgac 60
aagccaggct ttggtggcag catggacagt ggcctgtgc aggetgaaa             109

```

```

<210> 27
<211> 148
<212> DNA
<213> Homo sapiens

```

```

<400> 27
accatgacac cttcctgctg gccatgctcc tcagcgtcct gctgcctctg ctcccagggg 60
ccggcctggc ctggtgttgc taccgactcc caggagccca tctgcagcga tgcagctggg 120
gctgcagaag ggacctgctg tgcagtgg                                     148

```

```

<210> 28
<211> 92
<212> DNA
<213> Homo sapiens

```

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<400> 28
ccccaagat ggccacaca gggaccaccc cctgggcggc gttcacccca tggagttggg 60
ccccacagcc actggacagc cctggccctt gg                                     92

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```

<210> 29
<211> 72
<212> DNA
<213> Homo sapiens

```

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<400> 29
accctgagaa ctctcatgag cccagcagcc accctgagaa gcctctgcc a gcagtctgcg 60
ctgaccccca ag                                     72

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```

<210> 30
<211> 1031
<212> DNA
<213> Homo sapiens

```

```

<400> 30

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cagatcaagt ccagatgcc aagatcctgcc tctgggtgaga ggtagctcct aaaatgaaca 60
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aagacataaa a 1031

```

<210> 31  
 <211> 78  
 <212> DNA  
 <213> Homo sapiens

```

<400> 31
gtgtgccaga gcaggcgtg caggaagaat gccttcagg agcttcagcg ctgcctgact 60
gcctgccaca gccacggg 78

```

<210> 32  
 <211> 6  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: polyhistidine tag

```

<400> 32
His His His His His His
  1                      5

```

<210> 33  
 <211> 8  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: FLAG epitope tag

```

<400> 33
Asp Tyr Lys Asp Asp Asp Asp Lys
  1                      5

```

<210> 34  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 34  
aactcttgaa atgagaagcg tg

22

<210> 35  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 35  
aatatcatgc accatgaccc ac

22

<210> 36  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 36  
tggagtaagt attgtaaact at

22

<210> 37  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 37  
ggagcttatac ctggattatac ta

22

<210> 38  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 38  
agagccacac atccatgtcc tg 22

<210> 39  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 39  
aagccactct gtgaattgcc at 22

<210> 40  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 40  
gagtagtcgt agtaccagat gg 22

<210> 41  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 41  
gtctggcaat ggagcatgaa aa 22

<210> 42  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 42  
attagagcac atgaaggaaa gg 22

<210> 43

<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 43  
acactgcttt gggggacagg ct 22

<210> 44  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 44  
cacgacgcca cagagccagc tc 22

<210> 45  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 45  
aaccaccacg gattcacgct tc 22

<210> 46  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 46  
ataaccagat ggctgtgggt ca 22

<210> 47  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer



<400> 47  
atccccgcaa tgaaatagtt ta 22

<210> 48  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 48  
gttgagagcc cacttagata at 22

<210> 49  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 49  
gcattggggg aagccaggac at 22

<210> 50  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 50  
gccactagga ggcaatggca at 22

<210> 51  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 51  
cgacggcatc acggccatct gg 22

<210> 52  
<211> 22  
<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 52

tccaggctca ttcattttca tg

22

<210> 53

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 53

tgacatcaac ttctcctttc ct

22

<210> 54

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 54

agttgcagag acctagcctg tc

22

<210> 55

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 55

tctgggagag gacggagctg gc

22

<210> 56

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 56

tgtaggacta tattgctc

18

<210> 57  
 <211> 18  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Primer

<400> 57  
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<210> 58  
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<220>  
 <223> Description of Artificial Sequence: BstXI-linker  
 adapter

<400> 58  
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<210> 59  
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 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: BstXI-linker  
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<400> 59  
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<210> 60  
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<220>  
 <223> Description of Artificial Sequence: Synthetic  
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<400> 60  
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<210> 61

<211> 8  
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<210> 62  
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 <400> 62  
 His Glu Xaa Xaa His Xaa Xaa Gly Xaa Xaa His  
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<210> 63  
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<210> 64  
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 caggagacca cggaagatcg 20

<210> 65  
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<210> 66  
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<223> Description of Artificial Sequence: Primer

<400> 66  
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<210> 67  
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<223> Description of Artificial Sequence: Primer

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<210> 68  
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<223> Description of Artificial Sequence: Primer

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<210> 69  
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<210> 70

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<400> 71

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<210> 72

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<400> 72

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<210> 73

<211> 16

<212> DNA

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<223> Description of Artificial Sequence: Primer

<400> 73

ccacgaagga ccaccg

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<210> 74

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<210> 75  
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<210> 76  
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<210> 80  
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<210> 82  
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<400> 82  
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<400> 83  
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<210> 84  
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<210> 85  
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<210> 90  
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<223> Description of Artificial Sequence: Primer

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gtgttgctac cgactccag 20  
  
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<223> Description of Artificial Sequence: Primer

<400> 97  
gctcctcttg tccactctcc t 21

<210> 98  
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<210> 100  
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<210> 102  
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<210> 103  
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<400> 103  
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<210> 104  
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<400> 104  
aaagatggcc cacacagg 18

<210> 105  
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<400> 105  
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<210> 106  
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<210> 111  
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<400> 113  
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<210> 114  
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<400> 114  
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<210> 118  
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<223> Description of Artificial Sequence: Primer  
  
<400> 118  
gacgaccaa gaaacgcag 19  
  
<210> 119  
<211> 18  
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<220>  
<223> Description of Artificial Sequence: Primer  
  
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tgagcggaga gggcaagt 18



<210> 120  
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<223> Description of Artificial Sequence: Primer

<400> 120  
aaaccctcac cctgaacctt 20

<210> 121  
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<223> Description of Artificial Sequence: Primer

<400> 121  
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<210> 122  
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<223> Description of Artificial Sequence: Primer

<400> 122  
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<210> 123  
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<223> Description of Artificial Sequence: Primer

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<210> 124  
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<223> Description of Artificial Sequence: Primer

<400> 124  
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<210> 125  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 125  
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<210> 126  
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<223> Description of Artificial Sequence: Primer

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<210> 127  
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<223> Description of Artificial Sequence: Primer

<400> 127  
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<210> 128  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 128  
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<210> 129

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<220>  
<223> Description of Artificial Sequence: Primer

<400> 129  
cagcaagaca ccgcatctac 20

<210> 130  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 130  
gggacagagg gaaccattta 20

<210> 131  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 131  
ttccttctctg tttcttccca 20

<210> 132  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 132  
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<210> 133  
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<220>  
<223> Description of Artificial Sequence: Primer

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<210> 134  
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<400> 134  
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<210> 135  
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<400> 135  
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<210> 136  
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<223> Description of Artificial Sequence: Primer

<400> 136  
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<210> 137  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 137  
ctgggagtcg gtagcaaca 19

<210> 138  
<211> 18  
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<220>

<223> Description of Artificial Sequence: Primer

<400> 138

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<210> 139

<211> 20

<212> DNA

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<220>

<223> Description of Artificial Sequence: Primer

<400> 139

gcagcatggt acagggactg

20

<210> 140

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 140

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<210> 141

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 141

tgtcagacat ggccacagag

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<210> 142

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 142

agggtcctct tagctgccac

20

<210> 143  
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<212> DNA  
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<223> Description of Artificial Sequence: Primer

<400> 143  
aggccttggtc atttcctgtg 20

<210> 144  
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<210> 145  
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<223> Description of Artificial Sequence: Primer

<400> 145  
ctcagctccc ttctgtctc 19

<210> 146  
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<400> 146  
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<210> 147  
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gtaggtgtgc cagagcagg 19  
  
<210> 151  
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<210> 152  
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<223> Description of Artificial Sequence: Primer  
  
<400> 152  
caaagtcaca caacaagcgg 20

<210> 153  
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caggatcttg gcctctggac 20

<210> 154  
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<220>  
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<400> 154  
ctggcttgct acagaagggt 20

<210> 155  
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<220>  
<223> Description of Artificial Sequence: Primer  
  
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ctggagcaca gtggcagtta 20

<210> 156  
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<400> 156  
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<210> 157  
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<400> 157  
cctctcagga gtagaggccc 20

<210> 158  
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<400> 158  
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<210> 159  
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<400> 159  
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<210> 160  
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<400> 160  
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<210> 161  
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<212> DNA  
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caggactgca aacatcctga 20  
  
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<223> Description of Artificial Sequence: Primer  
  
<400> 163  
tccctgggtgc ttcccata 18  
  
<210> 164  
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aggcaggagg aagctgaat 19  
  
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cctcttgccc ctcttgct 18

<210> 166  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 166  
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<210> 167  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 167  
ggcctcgagt cccagtatatt 20

<210> 168  
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<220>  
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<400> 168  
agagcctcct gtctctccct 20

<210> 169  
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<220>  
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<400> 169  
tcgccctcag cttctcag 18

<210> 170  
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tcacgtgggt gcctctga 18  
  
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<400> 171  
gggttacttc ccctctctgg 20  
  
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ctgggctttc caccctgg 18  
  
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<223> Description of Artificial Sequence: Primer  
  
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<210> 250  
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containing SNP

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<210> 258  
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containing SNP

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<210> 259  
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<210> 260  
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<223> Description of Artificial Sequence: Sequence  
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&lt;400&gt; 260

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&lt;210&gt; 261

&lt;211&gt; 41

&lt;212&gt; DNA

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&lt;220&gt;

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&lt;210&gt; 262

&lt;211&gt; 41

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: Sequence  
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&lt;210&gt; 263

&lt;211&gt; 41

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: Sequence  
containing SNP

&lt;400&gt; 263

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&lt;210&gt; 264

&lt;211&gt; 41

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: Sequence  
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<210> 267  
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<210> 268  
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<210> 275  
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<400> 282  
ctgaggacca cacggggtgg tgggtggcgg ggtggtggtt g 41

<210> 283  
<211> 41  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Sequence  
containing SNP

<400> 283  
ggctggcagg ccgagcctag atggcagcca gagccccagg c 41

<210> 284  
<211> 41  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Sequence  
containing SNP

<400> 284  
ctttgctctg tcactcctgc ctcccttggg cgttcacatt c 41

<210> 285  
<211> 41  
<212> DNA  
<213> Homo sapiens

<400> 285  
gtgagctctg cccacccgac ccttccttgc cgtttgaatc c 41

<210> 286

<211> 41  
<212> DNA  
<213> Homo sapiens

<400> 286  
tggcgagggtt actcctacac cgggaggagc accgtcgggt c 41

<210> 287  
<211> 41  
<212> DNA  
<213> Homo sapiens

<400> 287  
ggctgctcac tattggggcc gcatcgcccc ctgtcccgct t 41

<210> 288  
<211> 41  
<212> DNA  
<213> Homo sapiens

<400> 288  
gccgcacgt cccctgtccc gcttgttggtg tgactttgcg c 41

<210> 289  
<211> 17  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 289  
gccgtcccac cccgtcg 17

<210> 290  
<211> 17  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 290  
ctcctctct tggcgac 17

<210> 291  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 291  
tccacactct ttcttgcc 18  
  
<210> 292  
<211> 20  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 292  
gctccacact ctttcttgcc 20  
  
<210> 293  
<211> 18  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 293  
tcaccaaggc tccttcct 18  
  
<210> 294  
<211> 21  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 294  
cagaagagac aggaattcac a 21  
  
<210> 295  
<211> 19  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 295  
tggaaaggaa cctgtggcc 19

<210> 296  
<211> 17  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 296  
gggttcggg gagcttg 17

<210> 297  
<211> 16  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 297  
gggttggggg actgtc 16

<210> 298  
<211> 16  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 298  
ctctgcgcgt ctggcg 16

<210> 299  
<211> 17  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 299  
gccgtccctc cccgtcg 17

<210> 300  
<211> 20  
<212> DNA  
<213> Artificial Sequence

<220>



<223> Description of Artificial Sequence: Primer

<400> 300

tcctcctcta ttggcgaccc

20

<210> 301

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 301

ctccacactt tttcttgccc a

21

<210> 302

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 302

gctccacact ctttcttgc

19

<210> 303

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 303

tcaccaagcc tccttcct

18

<210> 304

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 304

agaagagacg ggaattcac

19

<210> 305

<211> 17  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 305  
tggaaggag cctgtgg 17

<210> 306  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 306  
agggttcgt ggagcttg 19

<210> 307  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 307  
ggggttggag gactgtcc 18

<210> 308  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 308  
gctctgcgca tctggcg 18

<210> 309  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 309  
agtcaagcga ggggtgg 18

<210> 310  
<211> 16  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 310  
cctcagcgtc ctgctg 16

<210> 311  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 311  
aacaggaggt tccagtgg 18

<210> 312  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 312  
accagttttc ggcccttt 18

<210> 313  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 313  
ctgtcacccc cttgaagt 18

<210> 314  
<211> 16  
<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 314

tcagctgcgg tgctgg

16

<210> 315

<211> 15

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 315

gccttgggg atgga

15

<210> 316

<211> 16

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 316

tcctgctcc ttccag

16

<210> 317

<211> 16

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 317

actggacagc cctggc

16

<210> 318

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 318

ctgtgtggca gagagcca

19

<210> 319  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 319  
aattatgttt gtttcagag gc 22

<210> 320  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 320  
gaacttctag tgtggctct 19

<210> 321  
<211> 17  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 321  
ccaaggagg caggagt 17

<210> 322  
<211> 18  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 322  
agtcaagcgt gggggtgg 18

<210> 323  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 323  
ctcctcagca tcctgctgc 19  
  
<210> 324  
<211> 20  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 324  
gaacaggagt ttccagtggc 20  
  
<210> 325  
<211> 20  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 325  
caccagtttt tggccctttg 20  
  
<210> 326  
<211> 20  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 326  
ctgtcaccca cttgaagttc 20  
  
<210> 327  
<211> 18  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Description of Artificial Sequence: Primer  
  
<400> 327  
ggtcagctgt ggtgctgg 18

<210> 328  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 328  
aggccttggg agatgggat 19

<210> 329  
<211> 16  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 329  
tcctgccttc ttccag 16

<210> 330  
<211> 16  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 330  
actggacagt cctggc 16

<210> 331  
<211> 16  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 331  
tgtggcaggg agccca 16

<210> 332  
<211> 20  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 332  
attatgtttg cttgcagagg 20

<210> 333  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 333  
ggaacttcta atgtggctct g 21

<210> 334  
<211> 20  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: Primer

<400> 334  
cccaaggga gcaggagtga 20

<210> 335  
<211> 55  
<212> PRT  
<213> Homo sapiens

<400> 335  
Cys Cys Phe Ala His Asn Cys Ser Leu Arg Pro Gly Ala Gln Cys Ala  
1 5 10 15  
His Gly Asp Cys Cys Val Arg Cys Leu Leu Lys Pro Ala Gly Ala Leu  
20 25 30  
Cys Arg Gln Ala Met Gly Asp Cys Asp Leu Pro Glu Phe Cys Thr Gly  
35 40 45  
Thr Ser Ser His Cys Pro Pro  
50 55

<210> 336  
<211> 11  
<212> PRT  
<213> Homo sapiens

<400> 336  
Thr Met Ala His Glu Ile Gly His Ser Leu Gly



1' 5 10

<210> 337

<211> 86

<212> PRT

<213> Homo sapiens

<400> 337

Met Gly Trp Arg Pro Arg Arg Ala Arg Gly Thr Pro Leu Leu Leu Leu  
1 5 10 15

Leu Leu Leu Leu Leu Leu Trp Pro Val Pro Gly Ala Gly Val Leu Gln  
20 25 30

Gly His Ile Pro Gly Gln Pro Val Thr Pro His Trp Val Leu Asp Gly  
35 40 45

Gln Pro Trp Arg Thr Val Ser Leu Glu Glu Pro Val Ser Lys Pro Asp  
50 55 60

Met Gly Leu Val Ala Leu Glu Ala Glu Gly Gln Glu Leu Leu Leu Glu  
65 70 75 80

Leu Glu Lys Asn His Arg  
85

<210> 338

<211> 48

<212> PRT

<213> Homo sapiens

<400> 338

Met Gly Trp Arg Pro Arg Arg Ala Arg Gly Thr Pro Leu Leu Leu Leu  
1 5 10 15

Leu Leu Leu Leu Leu Leu Trp Pro Val Pro Gly Ala Gly Val Leu Gln  
20 25 30

Gly His Ile Pro Gly Gln Pro Val Thr Pro His Trp Val Leu Asp Gly  
35 40 45

<210> 339

<211> 178

<212> PRT

<213> Homo sapiens

<400> 339

Met Gly Trp Arg Pro Arg Arg Ala Arg Gly Thr Pro Leu Leu Leu Leu  
1 5 10 15

Leu Leu Leu Leu Leu Leu Trp Pro Val Pro Gly Ala Gly Val Leu Gln  
20 25 30

Gly His Ile Pro Gly Gln Pro Val Thr Pro His Trp Val Leu Asp Gly  
                   35                                  40                                  45  
 Gln Pro Trp Arg Thr Val Ser Leu Glu Glu Pro Val Ser Lys Pro Asp  
           50                                  55                                  60  
 Met Gly Leu Val Ala Leu Glu Ala Glu Gly Gln Glu Leu Leu Leu Glu  
   65                                  70                                  75                                  80  
 Leu Glu Lys Asn His Arg Leu Leu Ala Pro Gly Tyr Ile Glu Thr His  
                                   85                                  90                                  95  
 Tyr Gly Pro Asp Gly Gln Pro Val Val Leu Ala Pro Asn His Thr Val  
                   100                                  105                                  110  
 Arg Cys Phe His Gly Leu Trp Asp Ala Pro Pro Glu Asp His Cys His  
           115                                  120                                  125  
 Tyr Gln Gly Arg Val Arg Gly Phe Pro Asp Ser Trp Val Val Leu Cys  
   130                                  135                                  140  
 Thr Cys Ser Gly Met Ser Gly Leu Ile Thr Leu Ser Arg Asn Ala Ser  
  145                                  150                                  155                                  160  
 Tyr Tyr Leu Arg Pro Trp Pro Pro Arg Gly Ser Lys Asp Phe Ser Thr  
                                   165                                  170                                  175  
 His Glu

&lt;210&gt; 340

&lt;211&gt; 113

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 340

Met Gly Trp Arg Pro Arg Arg Ala Arg Gly Thr Pro Leu Leu Leu Leu  
   1                                  5                                  10                                  15  
 Leu Leu Leu Leu Leu Leu Trp Pro Val Pro Gly Ala Gly Val Leu Gln  
           20                                  25                                  30  
 Gly His Ile Pro Gly Gln Pro Val Thr Pro His Trp Val Leu Asp Gly  
           35                                  40                                  45  
 Gln Pro Trp Arg Thr Val Ser Leu Glu Glu Pro Val Ser Lys Pro Asp  
           50                                  55                                  60  
 Met Gly Leu Val Ala Leu Glu Ala Glu Gly Gln Glu Leu Leu Leu Glu  
   65                                  70                                  75                                  80  
 Leu Glu Lys Asn His Gly Leu Ile Thr Leu Ser Arg Asn Ala Ser Tyr  
                                   85                                  90                                  95

Tyr Leu Arg Pro Trp Pro Pro Arg Gly Ser Lys Asp Phe Ser Thr His  
                   100                                  105                                  110

Glu

<210> 341

<211> 165

<212> PRT

<213> Homo sapiens

<400> 341

Met Gly Trp Arg Pro Arg Arg Ala Arg Gly Thr Pro Leu Leu Leu Leu  
       1                                  5                                  10                                  15

Leu Leu Leu Leu Leu Leu Trp Pro Val Pro Gly Ala Gly Val Leu Gln  
                   20                                  25                                  30

Gly His Ile Pro Gly Gln Pro Val Thr Pro His Trp Val Leu Asp Gly  
                   35                                  40                                  45

Gln Pro Trp Arg Thr Val Ser Leu Glu Glu Pro Val Ser Lys Pro Asp  
       50                                  55                                  60

Met Gly Leu Val Ala Leu Glu Ala Glu Gly Gln Glu Leu Leu Leu Glu  
       65                                  70                                  75                                  80

Leu Glu Lys Asn His Arg Leu Leu Ala Pro Gly Tyr Ile Glu Thr His  
                   85                                  90                                  95

Tyr Gly Pro Asp Gly Gln Pro Val Val Leu Ala Pro Asn His Thr Asp  
                   100                                  105                                  110

His Cys His Tyr Gln Gly Arg Val Arg Gly Phe Pro Asp Ser Trp Val  
       115                                  120                                  125

Val Leu Cys Thr Cys Ser Gly Met Ser Gly Leu Ile Thr Leu Ser Arg  
       130                                  135                                  140

Asn Ala Ser Tyr Tyr Leu Arg Pro Trp Pro Pro Arg Gly Ser Lys Asp  
       145                                  150                                  155                                  160

Phe Ser Thr His Glu  
                                   165

<210> 342

<211> 168

<212> PRT

<213> Homo sapiens

<400> 342

Leu Ala Pro Gly Tyr Ile Glu Thr His Tyr Gly Pro Asp Gly Gln Pro  
       1                                  5                                  10                                  15

```

Val Val Leu Ala Pro Asn His Thr Asp His Cys His Tyr Gln Gly Arg
      20                      25                      30
Val Arg Gly Phe Pro Asp Ser Trp Val Val Leu Cys Thr Cys Ser Gly
      35                      40                      45
Met Ser Gly Leu Ile Thr Leu Ser Arg Asn Ala Ser Tyr Tyr Leu Arg
      50                      55                      60
Pro Trp Pro Pro Arg Gly Ser Lys Asp Phe Ser Thr His Glu Ile Phe
      65                      70                      75                      80
Arg Met Glu Gln Leu Leu Thr Trp Lys Gly Thr Cys Gly His Arg Asp
      85                      90                      95
Pro Gly Asn Lys Ala Gly Met Thr Ser Leu Pro Gly Gly Pro Gln Ser
      100                     105                     110
Arg Gly Arg Arg Lys Ala Arg Arg Thr Arg Lys Tyr Leu Glu Leu Tyr
      115                     120                     125
Ile Val Ala Asp His Thr Leu Phe Leu Thr Arg His Arg Asn Leu Asn
      130                     135                     140
His Thr Lys Gln Arg Leu Leu Glu Val Ala Asn Tyr Val Asp Gln Leu
      145                     150                     155                     160
Leu Arg Thr Leu Asp Ile Gln Val
      165

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<210> 343
<211> 167
<212> PRT
<213> Homo sapiens

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<400> 343
Ser Gly Tyr Cys Trp Asp Gly Ala Cys Pro Thr Leu Glu Gln Gln Cys
  1                      5                      10                      15
Gln Gln Leu Trp Gly Pro Gly Ser His Pro Ala Pro Glu Ala Cys Phe
      20                      25                      30
Gln Val Val Asn Ser Ala Gly Asp Ala His Gly Asn Cys Gly Gln Asp
      35                      40                      45
Ser Glu Gly His Phe Leu Pro Cys Ala Gly Arg Asp Ala Leu Cys Gly
      50                      55                      60
Lys Leu Gln Cys Gln Gly Gly Lys Pro Ser Leu Leu Ala Pro His Met
      65                      70                      75                      80
Val Pro Val Asp Ser Thr Val His Leu Asp Gly Gln Glu Val Thr Cys
      85                      90                      95

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Arg Gly Ala Leu Ala Leu Pro Ser Ala Gln Leu Asp Leu Leu Gly Leu  
 100 105 110

Gly Leu Val Glu Pro Gly Thr Gln Cys Gly Pro Arg Met Val Cys Asn  
 115 120 125

Ser Asn His Asn Cys His Cys Ala Pro Gly Trp Ala Pro Pro Phe Cys  
 130 135 140

Asp Lys Pro Gly Phe Gly Gly Ser Met Asp Ser Gly Pro Val Gln Ala  
 145 150 155 160

Glu Asn His Asp Thr Phe Leu  
 165

&lt;210&gt; 344

&lt;211&gt; 193

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 344

Ser Gly Tyr Cys Trp Asp Gly Ala Cys Pro Thr Leu Glu Gln Gln Cys  
 1 5 10 15

Gln Gln Leu Trp Gly Pro Gly Ser His Pro Ala Pro Glu Ala Cys Phe  
 20 25 30

Gln Val Val Asn Ser Ala Gly Asp Ala His Gly Asn Cys Gly Gln Asp  
 35 40 45

Ser Glu Gly His Phe Leu Pro Cys Ala Gly Arg Asp Ala Leu Cys Gly  
 50 55 60

Lys Leu Gln Cys Gln Gly Gly Lys Pro Ser Leu Leu Ala Pro His Met  
 65 70 75 80

Val Pro Val Asp Ser Thr Val His Leu Asp Gly Gln Glu Val Thr Cys  
 85 90 95

Arg Gly Ala Leu Ala Leu Pro Ser Ala Gln Leu Asp Leu Leu Gly Leu  
 100 105 110

Gly Leu Val Glu Pro Gly Thr Gln Cys Gly Pro Arg Met Val Cys Gln  
 115 120 125

Ser Arg Arg Cys Arg Lys Asn Ala Phe Gln Glu Leu Gln Arg Cys Leu  
 130 135 140

Thr Ala Cys His Ser His Gly Val Cys Asn Ser Asn His Asn Cys His  
 145 150 155 160

Cys Ala Pro Gly Trp Ala Pro Pro Phe Cys Asp Lys Pro Gly Phe Gly  
 165 170 175

Gly Ser Met Asp Ser Gly Pro Val Gln Ala Glu Asn His Asp Thr Phe  
 180 185 190

Leu

<210> 345

<211> 126

<212> PRT

<213> Homo sapiens

<400> 345

Ser Gly Tyr Cys Trp Asp Gly Ala Cys Pro Thr Leu Glu Gln Gln Cys  
 1 5 10 15

Gln Gln Leu Trp Gly Pro Asp Gly Gln Glu Val Thr Cys Arg Gly Ala  
 20 25 30

Leu Ala Leu Pro Ser Ala Gln Leu Asp Leu Leu Gly Leu Gly Leu Val  
 35 40 45

Glu Pro Gly Thr Gln Cys Gly Pro Arg Met Val Cys Gln Ser Arg Arg  
 50 55 60

Cys Arg Lys Asn Ala Phe Gln Glu Leu Gln Arg Cys Leu Thr Ala Cys  
 65 70 75 80

His Ser His Gly Val Cys Asn Ser Asn His Asn Cys His Cys Ala Pro  
 85 90 95

Gly Trp Ala Pro Pro Phe Cys Asp Lys Pro Gly Phe Gly Gly Ser Met  
 100 105 110

Asp Ser Gly Pro Val Gln Ala Glu Asn His Asp Thr Phe Leu  
 115 120 125

<210> 346

<211> 93

<212> PRT

<213> Homo sapiens

<400> 346

Ala Trp Cys Cys Tyr Arg Leu Pro Gly Ala His Leu Gln Arg Cys Ser  
 1 5 10 15

Trp Gly Cys Arg Arg Asp Pro Ala Cys Ser Gly Pro Lys Asp Gly Pro  
 20 25 30

His Arg Asp His Pro Leu Gly Gly Val His Pro Met Glu Leu Gly Pro  
 35 40 45

Thr Ala Thr Gly Gln Pro Trp Pro Leu Asp Pro Glu Asn Ser His Glu  
 50 55 60

Pro Ser Ser His Pro Glu Lys Pro Leu Pro Ala Val Ser Pro Asp Pro  
 65 70 75 80

Gln Ala Asp Gln Val Gln Met Pro Arg Ser Cys Leu Trp  
 85 90

<210> 347

<211> 236

<212> PRT

<213> Homo sapiens

<400> 347

Ser Gly Tyr Cys Trp Asp Gly Ala Cys Pro Thr Leu Glu Gln Gln Cys  
 1 5 10 15

Gln Gln Leu Trp Gly Pro Asp Gly Gln Glu Val Thr Cys Arg Gly Ala  
 20 25 30

Leu Ala Leu Pro Ser Ala Gln Leu Asp Leu Leu Gly Leu Gly Leu Val  
 35 40 45

Glu Pro Gly Thr Gln Cys Gly Pro Arg Met Val Cys Gln Ser Arg Arg  
 50 55 60

Cys Arg Lys Asn Ala Phe Gln Glu Leu Gln Arg Cys Leu Thr Ala Cys  
 65 70 75 80

His Ser His Gly Val Cys Asn Ser Asn His Asn Cys His Cys Ala Pro  
 85 90 95

Gly Trp Ala Pro Pro Phe Cys Asp Lys Pro Gly Phe Gly Gly Ser Met  
 100 105 110

Asp Ser Gly Pro Val Gln Ala Glu Asn His Asp Thr Phe Leu Leu Ala  
 115 120 125

Met Leu Leu Ser Val Leu Leu Pro Leu Leu Pro Gly Ala Gly Leu Ala  
 130 135 140

Trp Cys Cys Tyr Arg Leu Pro Gly Ala His Leu Gln Arg Cys Ser Trp  
 145 150 155 160

Gly Cys Arg Arg Asp Pro Ala Cys Ser Gly Pro Lys Asp Gly Pro His  
 165 170 175

Arg Asp His Pro Leu Gly Gly Val His Pro Met Glu Leu Gly Pro Thr  
 180 185 190

Ala Thr Gly Gln Pro Trp Pro Leu Asp Pro Glu Asn Ser His Glu Pro  
 195 200 205

Ser Ser His Pro Glu Lys Pro Leu Pro Ala Val Ser Pro Asp Pro Gln  
 210 215 220

Ala Asp Gln Val Gln Met Pro Arg Ser Cys Leu Trp  
 225 230 235

<210> 348

<211> 302

<212> PRT

<213> Homo sapiens

<400> 348

Ser Gly Tyr Cys Trp Asp Gly Ala Cys Pro Thr Leu Glu Gln Gln Cys  
 1 5 10 15

Gln Gln Leu Trp Gly Pro Gly Ser His Pro Ala Pro Glu Ala Cys Phe  
 20 25 30

Gln Val Val Asn Ser Ala Gly Asp Ala His Gly Asn Cys Gly Gln Asp  
 35 40 45

Ser Glu Gly His Phe Leu Pro Cys Ala Gly Arg Asp Ala Leu Cys Gly  
 50 55 60

Lys Leu Gln Cys Gln Gly Gly Lys Pro Ser Leu Leu Ala Pro His Met  
 65 70 75 80

Val Pro Val Asp Ser Thr Val His Leu Asp Gly Gln Glu Val Thr Cys  
 85 90 95

Arg Gly Ala Leu Ala Leu Pro Ser Ala Gln Leu Asp Leu Leu Gly Leu  
 100 105 110

Gly Leu Val Glu Pro Gly Thr Gln Cys Gly Pro Arg Met Val Cys Gln  
 115 120 125

Ser Arg Arg Cys Arg Lys Asn Ala Phe Gln Glu Leu Gln Arg Cys Leu  
 130 135 140

Thr Ala Cys His Ser His Gly Val Cys Asn Ser Asn His Asn Cys His  
 145 150 155 160

Cys Ala Pro Gly Trp Ala Pro Pro Phe Cys Asp Lys Pro Gly Phe Gly  
 165 170 175

Gly Ser Met Asp Ser Gly Pro Val Gln Ala Glu Asn His Asp Thr Phe  
 180 185 190

Leu Leu Ala Met Leu Leu Ser Val Leu Leu Pro Leu Leu Pro Gly Ala  
 195 200 205

Gly Leu Ala Trp Cys Cys Tyr Arg Leu Pro Gly Ala His Leu Gln Arg  
 210 215 220

Cys Ser Trp Gly Cys Arg Arg Asp Pro Ala Cys Ser Gly Pro Lys Asp  
 225 230 235 240



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<400> 349
Ser Gly Tyr Cys Trp Asp Gly Ala Cys Pro Thr Leu Glu Gln Gln Cys
 1      5      10      15
Gln Gln Leu Trp Gly Pro Asp Gly Gln Glu Val Thr Cys Arg Gly Ala
 20      25      30
Leu Ala Leu Pro Ser Ala Gln Leu Asp Leu Leu Gly Leu Gly Leu Val
 35      40      45
Glu Pro Gly Thr Gln Cys Gly Pro Arg Met Val Cys Gln Ser Arg Arg
 50      55      60
Cys Arg Lys Asn Ala Phe Gln Glu Leu Gln Arg Cys Leu Thr Ala Cys
 65      70      75      80
His Ser His Gly Val Cys Asn Ser Asn His Asn Cys His Cys Ala Pro
 85      90      95
Gly Trp Ala Pro Pro Phe Cys Asp Lys Pro Gly Phe Gly Gly Ser Met
 100      105      110
Asp Ser Gly Pro Val Gln Ala Glu Asn His Asp Thr Phe Leu Leu Ala
 115      120      125
Met Leu Leu Ser Val Leu Leu Pro Leu Leu Pro Gly Ala Gly Leu Ala
 130      135      140
Trp Cys Cys Tyr Arg Leu Pro Gly Ala His Leu Gln Arg Cys Ser Trp
 145      150      155      160
Gly Cys Arg Arg Asp Pro Ala Cys Ser Gly Pro Lys Asp Gly Pro His
 165      170      175
Arg Asp His Pro Leu Gly Gly Val His Pro Met Glu Leu Gly Pro Thr
 180      185      190

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Ala Thr Gly Gln Pro Trp Pro Leu Asp Pro Glu Asn Ser His Glu Pro  
195 200 205

Ser Ser His Pro Glu Lys Pro Leu Pro Ala Val Ser Pro Asp Pro Gln  
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<211> 339

<212> DNA

<213> Homo sapiens

<400> 350

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<211> 225

<212> DNA

<213> Homo sapiens

<400> 351

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<210> 352

<211> 562

<212> DNA

<213> Homo sapiens

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 <212> DNA  
 <213> Homo sapiens

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 catatccctg ggcagccagt caccgccgac tgggtcctgg atggacaacc ctggcgccacc 180  
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 <212> DNA  
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<400> 356

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&lt;210&gt; 357

&lt;211&gt; 581

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 357

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&lt;210&gt; 358

&lt;211&gt; 380

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 358

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&lt;210&gt; 359

&lt;211&gt; 324

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 359

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gaacagattt aaagacaggt ggcc

324

&lt;210&gt; 360

&lt;211&gt; 753

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 360

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&lt;210&gt; 361

&lt;211&gt; 1154

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 361

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&lt;210&gt; 362

&lt;211&gt; 953

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 362

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&lt;210&gt; 363

&lt;211&gt; 812

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 363

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Leu Leu Leu Leu Leu Leu Trp Pro Val Pro Gly Ala Gly Val Leu Gln
 20             25             30

Gly His Ile Pro Gly Gln Pro Val Thr Pro His Trp Val Leu Asp Gly
 35             40             45

Gln Pro Trp Arg Thr Val Ser Leu Glu Glu Pro Val Ser Lys Pro Asp
 50             55             60

Met Gly Leu Val Ala Leu Glu Ala Glu Gly Gln Glu Leu Leu Leu Glu
 65             70             75             80

Leu Glu Lys Asn His Arg Leu Leu Ala Pro Gly Tyr Ile Glu Thr His
 85             90             95

Tyr Gly Pro Asp Gly Gln Pro Val Val Leu Ala Pro Asn His Thr Asp
100            105            110

His Cys His Tyr Gln Gly Arg Val Arg Gly Phe Pro Asp Ser Trp Val
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Val Leu Cys Thr Cys Ser Gly Met Ser Gly Leu Ile Thr Leu Ser Arg
130            135            140

Asn Ala Ser Tyr Tyr Leu Arg Pro Trp Pro Pro Arg Gly Ser Lys Asp

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Leu Pro Gly Gly Pro Gln Ser Arg Gly Arg Arg Glu Ala Arg Arg Thr						
		195		200		205
Arg Lys Tyr Leu Glu Leu Tyr Ile Val Ala Asp His Thr Leu Phe Leu						
		210		215		220
Thr Arg His Arg Asn Leu Asn His Thr Lys Gln Arg Leu Leu Glu Val						
		225		230		235
Ala Asn Tyr Val Asp Gln Leu Leu Arg Thr Leu Asp Ile Gln Val Ala						
		245		250		255
Leu Thr Gly Leu Glu Val Trp Thr Glu Arg Asp Arg Ser Arg Val Thr						
		260		265		270
Gln Asp Ala Asn Ala Thr Leu Trp Ala Phe Leu Gln Trp Arg Arg Gly						
		275		280		285
Leu Trp Ala Gln Arg Pro His Asp Ser Ala Gln Leu Leu Thr Gly Arg						
		290		295		300
Ala Phe Gln Gly Ala Thr Val Gly Leu Ala Pro Val Glu Gly Met Cys						
		305		310		315
Arg Ala Glu Ser Ser Gly Gly Val Ser Thr Asp His Ser Glu Leu Pro						
		325		330		335
Ile Gly Ala Ala Ala Thr Met Ala His Glu Ile Gly His Ser Leu Gly						
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Gly Gly Cys Val Met Ala Ala Ala Thr Gly His Pro Phe Pro Arg Val						
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Phe Ser Ala Cys Ser Arg Arg Gln Leu Arg Ala Phe Phe Arg Lys Gly						
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Gly Gly Ala Cys Leu Ser Asn Ala Pro Asp Pro Gly Leu Pro Val Pro						
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Pro Ala Leu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp						
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Cys Gly Pro Gly Gln Glu Cys Arg Asp Leu Cys Cys Phe Ala His Asn						
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Cys Ser Leu Arg Pro Gly Ala Gln Cys Ala His Gly Asp Cys Cys Val  
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 Pro Asp Val Tyr Leu Leu Asp Gly Ser Pro Cys Ala Arg Gly Ser Gly  
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Trp Gly Cys Arg Arg Asp Pro Ala Cys Ser Gly Pro Lys Asp Gly Pro  
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His Arg Asp His Pro Leu Gly Gly Val His Pro Met Glu Leu Gly Pro  
755 760 765

Thr Ala Thr Gly Gln Pro Trp Pro Leu Asp Pro Glu Asn Ser His Glu  
770 775 780

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<210> 364

<211> 21960

<212> DNA

<213> Mus sp.

<400> 364

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&lt;400&gt; 365

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&lt;400&gt; 366

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Asp Ser Val Leu Val Ala Leu Glu Ala Glu Gly Gln Asp Leu Leu Leu
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Glu Leu Glu Lys Lys His Lys Leu Leu Ala Pro Gly Tyr Thr Glu Thr
                85                      90                      95

His Tyr Arg Pro Asp Gly His Pro Val Val Leu Ser Pro Asn His Thr
                100                     105                     110

Asp His Cys Gln Tyr His Gly Arg Val Arg Gly Phe Arg Glu Ser Trp
                115                     120                     125

Val Val Leu Ser Thr Cys Ser Gly Met Ser Gly Leu Ile Val Leu Ser
  130                     135                     140

Ser Lys Val Ser Tyr Tyr Leu Gln Pro Arg Thr Pro Gly Asp Thr Lys
  145                     150                     155                     160

Asp Phe Pro Thr His Glu Ile Phe Arg Met Glu Gln Leu Phe Thr Trp
                165                     170                     175

Arg Gly Val Gln Arg Asp Lys Asn Ser Gln Tyr Lys Ala Gly Met Ala
                180                     185                     190

Ser Leu Pro His Val Pro Gln Ser Arg Val Arg Arg Glu Ala Arg Arg
  195                     200                     205

Ser Pro Arg Tyr Leu Glu Leu Tyr Ile Val Ala Asp His Thr Leu Asn
  210                     215                     220

Leu Asn His Thr Arg Gln Arg Leu Leu Glu Val Ala Asn Cys Val Asp

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Val Trp Thr Glu Gln Asp Leu Ser Arg Ile Thr Gln Asp Ala Asn Glu						
		260		265		270
Thr Leu Trp Ala Phe Leu Gln Trp Arg Arg Gly Val Trp Ala Arg Arg						
		275		280		285
Pro His Asp Ser Thr Gln Leu Leu Thr Gly Arg Thr Phe Gln Gly Thr						
		290		295		300
Thr Val Gly Leu Ala Pro Val Glu Gly Ile Cys Arg Ala Glu Ser Ser						
		305		310		315
Gly Gly Val Ser Thr Asp His Ser Glu Leu Pro Ile Gly Thr Ala Ala						
		325		330		335
Thr Met Ala His Glu Ile Gly His Ser Leu Gly Leu His His Asp Pro						
		340		345		350
Glu Gly Cys Cys Val Gln Ala Asp Ala Glu Gln Gly Gly Cys Val Met						
		355		360		365
Glu Ala Ala Thr Gly His Pro Phe Pro Arg Val Phe Ser Ala Cys Ser						
		370		375		380
Arg Arg Gln Leu Arg Thr Phe Phe Arg Lys Gly Gly Gly Pro Cys Leu						
		385		390		395
Ser Asn Thr Ser Ala Pro Gly Leu Leu Val Leu Pro Ser Arg Cys Gly						
		405		410		415
Asn Gly Phe Leu Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Gly Gln						
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Lys Cys Pro Asp Pro Cys Cys Phe Ala His Asn Cys Ser Leu Arg Ala						
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Gly Ala Gln Cys Ala His Gly Asp Cys Cys Ala Lys Cys Leu Leu Lys						
		450		455		460
Ser Ala Gly Thr Pro Cys Arg Pro Ala Ala Thr Asp Cys Asp Leu Pro						
		465		470		475
Glu Phe Cys Thr Gly Thr Ser Pro Tyr Cys Pro Ala Asp Val Tyr Leu						
		485		490		495
Leu Asp Gly Ser Pro Cys Ala Glu Gly Arg Gly Tyr Cys Leu Asp Gly						
		500		505		510
Trp Cys Pro Thr Leu Glu Gln Gln Cys Gln Gln Leu Trp Gly Pro Gly						
		515		520		525

Ser Lys Pro Ala Pro Glu Pro Cys Phe Gln Gln Met Asn Ser Met Gly  
 530 535 540  
 Asn Ser Gln Gly Asn Cys Gly Gln Asp His Lys Gly Ser Phe Leu Pro  
 545 550 555 560  
 Cys Ala Gln Arg Asp Ala Leu Cys Gly Lys Leu Leu Cys Gln Gly Gly  
 565 570 575  
 Glu Pro Asn Pro Leu Val Pro His Ile Val Thr Met Asp Ser Thr Ile  
 580 585 590  
 Leu Leu Glu Gly Arg Glu Val Val Cys Arg Gly Ala Phe Val Leu Pro  
 595 600 605  
 Asp Ser His Leu Asp Gln Leu Asp Leu Gly Leu Val Glu Pro Gly Thr  
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 Gly Cys Gly Pro Arg Met Val Cys Gln Asp Arg His Cys Gln Asn Ala  
 625 630 635 640  
 Thr Ser Gln Glu Leu Glu Arg Cys Leu Thr Ala Cys His Asn Gly Gly  
 645 650 655  
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 Pro Phe Cys Asp Lys Pro Gly Leu Gly Gly Ser Val Asp Ser Gly Pro  
 675 680 685  
 Ala Gln Ser Ala Asn Arg Asp Ala Phe Pro Leu Ala Met Leu Leu Ser  
 690 695 700  
 Phe Leu Leu Pro Leu Leu Pro Gly Ala Gly Leu Ala Trp Cys Tyr Tyr  
 705 710 715 720  
 Gln Leu Pro Thr Phe Cys His Arg Arg Gly Leu Cys Cys Arg Arg Asp  
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 740 745 750  
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<210> 397

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